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Butyryl-cholinesterase deficiency: A case report of delayed recovery after general anaesthesia

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ABSTRACT

Background: Apnoea and prolonged paralysis after succinylcholine administration is not uncommon occurrence in anaesthetic practice. It occurs due to inherited or acquired deficiency of butyrylcholinesterase.
Case report: Here we report a case of succinylcholine apnoea for 2 h in a 5 years old girl who was anaesthetized for bronchoscopic extraction of a foreign body. She was subsequently kept on assisted ventilation. She recovered few minutes after I.V. atropine and naloxone. Laboratory investigation revealed low cholinesterase activity. Thus the girl was given 150 mL fresh frozen plasma. She has been discharged the next day after complete recovery.
Conclusion: As the genetic analysis was not available to confirm the diagnosis of atypical variant of cholinesterase. The family was advised to submit serum samples for assessment of cholinesterase activity and avoid exposure to cholinesterase inhibitors. Moreover, clear instructions were given to the family so they can warn the anaesthetists in case any family member undergoes general anesthesia for any reason in the future. Furthermore, they must be strongly advised to avoid exposure to anticholinesterases as they might have heightened sensitivity to these agents. It should be emphasized that Naloxone and atropine could help speed up recovery in such cases.

1. Introduction

Prolonged unconsciousness after anaesthesia is considered one of the real challenges that most anaesthetists face [1]. It was first described in 1953 following injection of succinylcholine. The condition of succinylcholine apnea is believed to occur in 1 in 1800 administrations of succinylcholine [2,3]. Approximately 65 % of these are caused by decreased succinylcholine hydrolysis by abnormal butyrylcholinesterase enzyme (BChE) variants with decreased enzymatic activity or decreased protein stability leading to lower effective serum levels [4]. BChE is also known as pseudocholinesterase (PChE), false cholinesterase, serum cholinesterase and plasma cholinesterase. It is the sister enzyme of acetylcholinesterase (AChE) [5]. It is synthesized in the liver and present in most tissues except erythrocytes. Although its potential functions are still debated, it is well known for its role in catalyzing the hydrolysis of choline esters such as succinylcholine and mivacurium. BChE enzyme deficiency is either acquired or genetic. The acquired causes of reduced activity of BChE include hepatic diseases, renal disease, malnutrition, pregnancy, HELLP syndrome, malignancies, burns, cardiopulmonary bypass and leprosy. Interested readers are referred to this review [4]. In addition, anticholinesterases reduce the enzyme activity and result in prolonged apnoea/paralysis after succinylcholine administration. Moreover, the following drugs have been found to suppress PChE activity: cocaine, pancuromium, aspirin, sertraline, cyclophosphamide, tacrine, contraceptives, phenelzine, bambuterol and metoclopramide. Interested readers are referred to this review [6].

As regards BChE genetic deficiency, it was described by Kalow and Genest in 1957 [7]. The BChE gene is located on chromosome 3 at 3q26.1−26.2. It consists of 3 coding exons and spans approximately 64 kb. The mode of inheritance of BChE deficiency is autosomal recessive. It has been estimated that nearly a quarter of the human population carries at least one variant BCHE allele [8]. Approximately 70 natural mutations of human BChE have been documented so far [9]. Over 20 of these variants adversely affect the enzyme in terms of activity and concentration. These variants have been divided into qualitative variants that alter the enzyme hydrolytic activity and quantitative variants with reduced enzyme concentration but normal activity. The qualitative variants include the atypical (A) [10], silent (S) variants [11], and fluoride-resistant (F) [12] among others, whereas the quantitative variants include J [13], H [14] and K variants among others [15]. Although the majority of BChE mutations are a rarity, the two of them are relatively common the A and K variants. K-variant in honor of Werner Kalow

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[c.1699 G > A, Ala567Thr (A567 T), rs1803274] is the most common BChE variant with 33 % reduction of plasma BChE activity. Also, the atypical variant of BChE [c.209 A > G, Asp70Gly (D70 G), rs1799807], which is the variant most frequently associated with prolonged response to muscle relaxants, has both reduced activity and enzyme concentration [16]. The A variant results in approximately 2 h-long of succinylcholine apnoea compared to only 3–5 minute-long paralysis with the usual (U) allele [17]. The S variant results in apnoea of 3−4 h long or even longer [2,18]. Fortunately, the A or S variants are rare, however, heterozygotes are much more common (4% of the general population) and could present with varying degrees of apnea depending on their specific allelic combination that impact their serum BChE activity [4, 18]. Interested readers are referred to this review [16]. Interestingly enough, the discovery of new mutations is ongoing. For instance, a new double heterozygous recessive mutation was found to be associated with both BChE deficiency and intellectual disability phenotype [19]. Moreover, A patient with marked deficiency in BChE activity was found to have three point mutations in a compound heterozygous state: two were previously characterized (A and K variants) and the third one was newly identified where mis-sense mutation at amino acid residue 204 (c.695 T > A, Val204Asp, GenBank Accession #KJ513459). Although this point mutation (Val204Asp) is far from the active site, it leads to a "silent" BChE phenotype [20]. Furthermore, mutations near residue Val204 have previously been described: Ala199Val [21], Ala201Thr [22] and Ser203Pro [23]. These mutations result in a silent phenotype too of yet to be determined mechanisms.

It is noteworthy that the genetic variants with abnormally low levels of BChE enzyme including the A, K, and S variants are predicted to be unusually sensitive to toxicity from low doses of nerve agents [16]. It could be plausibly argued that besides their heightened sensitivity to the muscle relaxants, individuals deficient in BChE might be unusually sensitive to anticholinesterases. In fact this is a question that needs further research to be appropriately addressed.

2. Case study

We present a case of delayed recovery after succinylcholine administration. This previously healthy 5 year old girl was transferred to the emergency hospital with a history of an acute onset of choking, severe coughing, hoarseness of voice, shortness of breath, cyanosis and wheezing. On examination, patients had stridor, wheezing, decreased breath sounds in the right lung, following suspected foreign body aspiration. A chest X-ray was ordered, however it did not show a foreign body. The surgical team decided to take the girl to the operative theatre for bronchoscopy. After succinylcholine administration and anesthesia, the girl underwent a prompt exploratory bronchoscopy which did not reveal any foreign body. Upon reversal from anesthesia, the girl could not breathe spontaneously and her pupils were constricted. The girl remained apnoeic for two hours. Adequate ventilation was maintained. The anaesthetist raised the possibility that the girl could have been exposed to either organophosphorus or opiate toxicity as she was living in a neighborhood of drug dealers. Clinical toxicology has been consulted. Toxicology screen and measurement of cholinesterase activity were ordered. A thorough history had been taken from the girl's father. The girl had no signs of hepatic injury, malnutrition or any other severe diseases and the drug history was unremarkable. Consequently, it has been concluded that this case could belong to the category of genetic deficiency of BChE. The girl started sluggish spontaneous breathing 5 min after I.V. administration of 1 mg Atropine sulphate and 0.4 mg Naloxone HCl. Laboratory results came back with negative toxicology screen however, cholinesterase activity was very low. The girl received 150 mL fresh frozen plasma and put under observation for 24 h until complete recovery. The girl discharged home next day.

3. Discussion

Foreign body aspiration by children is a serious and life-threatening situation that requires early recognition and emergency interference. Typically, there is a history of choking, although the classic clinical presentation, with coughing, wheezing, and diminished air entry, is seen in less than 40 % of the patients [24]. Other presenting symptoms include cyanosis, fever, and stridor. Moreover, it can present with a great variety of symptoms of varying severity including respiratory distress, chronic coughing, atelectasis, recurrent pneumonia, and even death. On the other hand, it can be completely asymptomatic [25,26]. The diagnosis needs high index of suspicion together with thorough history, examination and radiologic investigation. However, the presenting symptoms are usually nonspecific, and the chest radiologic findings are frequently normal or show abnormalities that are not characteristic for foreign body aspiration. Therefore, children presenting with suspicious history or symptoms should undergo prompt bronchoscopy regardless of the radiologic findings [26,27].

In our case, the 5 year old girl presented with history and symptoms suggestive of foreign body aspiration. In spite of the normal findings on chest X-ray, the possibility of foreign body aspiration couldn't be excluded. Therefore, the surgical team decided to go for bronchoscopy which didn't reveal any foreign body. The problem began when the anesthetist started weaning the girl from the ventilator. The pupillary constriction and the fact that the girl were living in the neighborhood of drug dealers made the anesthetist to consult clinical toxicology to investigate the likelihood of opioid and/or organophosphorus poisoning in addition to succinylcholine apnoea. Blood and urine samples were sent for toxicology screen and measurement of cholinesterase activity, while the girl was still on mechanical ventilation. The patient's medical history was reviewed with her father. There was no medical history of significance, drug history or family history of similar presentation after anaesthesia. Therefore, we were left with only one possibility that the diagnosis is delayed recovery after succinylcholine due to genetic deficiency of BCHE. We decided on I.V. administration of 1 mg atropine sulphate and 0.4 mg Naloxone which were followed by the return of sluggish spontaneous respiration. In addition, the girl was transfused with 150 mL of fresh frozen plasma and was closely monitored for 24 h until complete recovery and discharge on the following day.

It has to be emphasized that, although the nonfunctional or deficient serum BChE can be replaced by the normal "U" variant of the enzyme present in blood products such as stabilized serum [28], fresh frozen plasmaor the purified enzyme, this treatment carries the usual risks of blood-borne pathogens and the common transfusion associated complications [4]. Given the seriousness of the succinylcholine apnoea and the lack of a reversing agent, few studies proved that purified recombinant human BChE would serve as an ideal antidote for SC apnea [29, 30]. Moreover, another recent study provided a proof of principle that administration of plant-produced recombinant human BChE can reverse SC-induced apnea [6].

In conclusion, whenever the delayed recovery after anesthesia is suspected to be due to pseudocholinesterase deficiency, the following measures must be strictly applied: 1) continued ventilatory support till recovery or the suspected anesthetic is hydrolyzed, 2) The patient's and all the family members' enzymes level must be determined, 3) Further exposure to the suspected anesthetics must be avoided, 4) Caregivers must be adequately notified of the patient enzyme deficiency for any subsequent hospitalization. Moreover, it is of utmost importance that the patient and all the family members must be genetically screened for variants of human BChE. Furthermore, it would be wise to warn the patient to avoid exposure to anticholinesterases.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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