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

Ahmed Al-Emam

**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.

**Keywords**: Butyrylcholinesterase; Case report; Delayed recovery; General anaesthesia

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. 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, pancuronium, 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

**ARTICLE INFO**

Handling Editor: Dr. Aristidis Tsatsakis

**Keywords**: Butyryl-cholinesterase; Case report; Delayed recovery; General anaesthesia

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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.

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wheezing. On examination, patients had stridor, wheezing, decreased to muscle relaxants, has both reduced activity and enzyme concentra-
tion. The A variant results in approximately 2 h-long of succinyl-
choline 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,
16]. 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
usually 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.

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 pre-
senting 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 present-
ning with suspicious history or symptoms should undergo prompt bron-
choscopy 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 pulmonary
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 defi-
ciency 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
untily 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 com-
plications [4]. Given the seriousness of the succinylcholine apnoea and
the lack of a reversing agent, few studies proved that purified recom-
binant 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.

Fund

None.
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.

Acknowledgement

None.

References

[1] R.C.F. Sinclair, J.F. Richard, Delayed recovery of consciousness after anaesthesia. Continuing Education in Anaesthesia, Crit. Care Pain Med. 6 (3) (2006) 114–118, https://doi.org/10.1093/bjaacep/mkl020.

[2] I. Manoharan, S. Wieseler, P.G. Layer, O. Lockridge, R. Boopathy, Naturally occurring mutation Leu307Pro of human butyrylcholinesterase in a Brazilian blood donor sample, Mol. Genet. Metab. 84 (4) (2005) 349–353, https://doi.org/10.1016/j.ymgme.2005.03.003.

[3] H.W. Bauld, P.F. Gibson, P.J. Jebson, S.S. Brown, Aetiology of prolonged apnoea after suxamethonium, Br. J. Anaesth. 46 (4) (1974) 273–281, https://doi.org/10.1093/bja/46.4.273.

[4] F.K. Soliday, Y.P. Conley, R. Henker, Pseudocholinesterase deficiency: a comprehensive review of genetic, acquired, and drug influences, AANA J. 78 (4) (2010) 313–320. PMID: 20879632.

[5] A. FORBAT, H. LEHMANN, E. SILK, Prolonged apnoea following injection of suxamethonium, Lancet 265 (6795) (1953) 1067–1068. PMID: 2324074.

[6] B.C. Geyer, K.E. Larrimore, J. Kilbourne, L. Kannan, T.S. Mor, Reversal of succinylcholine induced apnea with an organophosphate scavenging recombinant butyrylcholinesterase, PLoS One 8 (3) (2013) e59159, https://doi.org/10.1371/journal.pone.0059159. Epub 2013 Mar 11. PMID: 23536865.

[7] W. KALOW, K. GENEST, A method for the detection of atypical forms of human serum cholinesterase; determination of dibucaine numbers, Can. J. Biochem. Physiol. 35 (6) (1957) 339–346, https://doi.org/10.1139/y57-041. PMID: 15781196.

[8] R.L. Souza, L.R. Mikami, B.N. La Du, Identification of 12 silent alleles of the human butyrylcholinesterase gene and phenotype identified in a child with low butyrylcholinesterase activity: a case report, BMC Med. Genet. 19 (1) (2018) 58. https://doi.org/10.1186/s12881-018-0561-5. PMID: 29631548. PMCID: PMC5891924.

[9] J. Viby-Mogensen, H.K. Hanel, Prolonged apnoea after suxamethonium: an analysis of the first 225 cases reported to the Danish Cholinesterase Research Unit, Acta Anaesthesiol. Scand. 22 (4) (1978) 371–380. https://doi.org/10.1111/j.1399-6576.1981.tb01131.x. PMID: 726855.

[10] R. Yu, Y. Guo, Y. Dan, W. Tan, Q. Mao, G. Deng, A novel mutation in the BCHE gene and phenotype identified in a child with low butyrylcholinesterase activity: a case report, BMC Med. Genet. 19 (1) (2018) 58. https://doi.org/10.1186/s12881-018-0561-5. PMID: 29631548. PMCID: PMC5891924.

[11] H. Delacour, S. Lushchekina, I. Mabboux, A. Bouquet, F. Ceppa, L.M. Schopfer, O. Lockridge, P. Masson, Characterization of a novel BCHE ‘silent’ allele: point mutation (p.Val204Asp) causes loss of activity and prolonged apnea with suxamethonium, PLoS One 9 (7) (2014) e101552, https://doi.org/10.1371/journal.pone.0101552. PMID: 25054547. PMCID: PMC4108472.

[12] N. Sakamoto, K. Hidaka, T. Fujisawa, M. Maeda, I. Iuchi, Identification of a point mutation associated with a silent phenotype of human serum butyrylcholinesterase-a case of familial cholinesterasemia, Clin. Chim. Acta 320. PMID: 20879632.

[13] S.L. Primo-Parmo, C.F. Bartels, B. Wiersema, A.F. van der Spek, J.W. Inizs, B.N. La Du, Characterization of 12 silent alleles of the human butyrylcholinesterase (BCHE) gene, Am. J. Hum. Genet. 58 (1) (1996) 52–64. PMID: 8554668; PMCID: PMC1914969.

[14] K. Hidaka, Y. Watanabe, M. Tomita, N. Ueda, M. Higashi, Y. Minatogawa, I. Iuchi, Gene analysis of genomic DNA from stored serum by polymerase chain reaction: identification of three missense mutations in patients with cholinesterasemia and AB0 genotyping, Clin. Chim. Acta 303 (1–2) (2001) 61–67, https://doi.org/10.1016/s0009-8981(00)00375-2. PMID: 11630324.

[15] J.T. Zerella, M. Dimler, L.C. McGill, K.J. Pippus, Foreign body aspiration in children: value of radiography and complications of bronchoscopy, J. Pediatr. Surg. 29 (5) (1994) 682–684, https://doi.org/10.1016/0022-3468(94)90740-4. PMID: 8035283.

[16] J. Viby-Mogensen, H.K. Hanel, Prolonged apnoea after suxamethonium: an analysis of the first 225 cases reported to the Danish Cholinesterase Research Unit, Acta Anaesthesiol. Scand. 22 (4) (1978) 371–380. https://doi.org/10.1111/j.1399-6576.1981.tb01131.x. PMID: 726855.

[17] J. Hidaka, Y. Watanabe, M. Tomita, N. Ueda, M. Higashi, Y. Minatogawa, I. Iuchi, Gene analysis of genomic DNA from stored serum by polymerase chain reaction: identification of three missense mutations in patients with cholinesterasemia and AB0 genotyping, Clin. Chim. Acta 303 (1–2) (2001) 61–67, https://doi.org/10.1016/s0009-8981(00)00375-2. PMID: 11630324.

[18] R.E. Black, D.G. Johnson, M.E. Mathlak, Bronchoscopic removal of aspirated foreign bodies in children, J. Pediatr. Surg. 29 (5) (1994) 682–684, https://doi.org/10.1016/0022-3468(94)90740-4. PMID: 8035283.

[19] J. Viby-Mogensen, H.K. Hanel, Prolonged apnoea after suxamethonium: an analysis of the first 225 cases reported to the Danish Cholinesterase Research Unit, Acta Anaesthesiol. Scand. 22 (4) (1978) 371–380. https://doi.org/10.1111/j.1399-6576.1981.tb01131.x. PMID: 726855.

[20] J. Viby-Mogensen, H.K. Hanel, Prolonged apnoea after suxamethonium: an analysis of the first 225 cases reported to the Danish Cholinesterase Research Unit, Acta Anaesthesiol. Scand. 22 (4) (1978) 371–380. https://doi.org/10.1111/j.1399-6576.1981.tb01131.x. PMID: 726855.