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The diving bell and the butterfly

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When patients undergo general anaesthesia, they might feel as if they are entering an oxygenated and carefully monitored diving bell. They entrust their lives to the anaesthetist, who lowers them gently into the depths of oblivion for the duration of the surgery, before allowing them to emerge safely with awareness restored. When patients express dread of awakening prematurely in the diving bell, analogous to taphephobia (a fear of being buried alive), we comfort them that such iatrogenic locked-in experiences are vanishingly rare. Based on innovative research in this issue of the *British Journal of Anaesthesia* by Thomsen and colleagues[1 2] and literature regarding the prevalence of postoperative weakness in general,[3–6] such reassurance might be overly sanguine.

Thomsen and colleagues[1 2] conducted complementary studies using data from the Danish Cholinesterase Research Unit. Taking advantage of this registry was an inspired investigative decision because it provides a model for intraoperative neuromuscular block with a high likelihood of residual weakness upon emergence from anaesthesia. In one of the studies, the researchers discovered that, predictably, many patients with atypical forms of butyrylcholinesterase (BChE) were weak at the end of the surgery and had a high incidence of respiratory complications. What was perhaps more revealing in their findings was that, despite being contacted years after their anaesthesia, half of the patients who were successfully interviewed (35 of 70) reported postoperative awareness. Notably, 86% (30 of 35) of these patients with awareness reported distress regarding the experience of being awake and profoundly weak following their surgery. This finding should alter our perspectives and priorities. Anaesthetists have historically focused on the prevention of intraoperative awareness, but this research establishes the importance to our patients of distressing awareness with profound weakness that can occur after surgery. Encouraging in the findings of Thomsen and colleagues,[1 2] however, was that when intraoperative neuromuscular monitoring was used, both postoperative respiratory complications and distressing postoperative awareness had a much lower incidence.

One of the earliest descriptions of succinylcholine administration to humans comes from Otto Mayrhofer, who in 1952 described his self-experiments with this depolarizing neuromuscular blocking agent.[7] Mayrhofer[7] extols one of the benefits of succinylcholine by stating, 'It is destroyed in the body so rapidly—apparently by enzymatic hydrolysis—that no antidote is needed'. Mayrhofer[7] describes his experiences of awake paralysis as follows: 'double vision, ptosis, general muscle weakness, and intercostal paralysis, followed about 30 s later by total paralysis, including the

diaphragm'. Despite this seemingly harrowing account, Mayrhofer does not describe being distressed, probably because he anticipated these sensations and the duration was brief. With widespread usage of succinylcholine, however, it was soon discovered that about one in 2000 people experience prolonged paralysis or 'scoline apnoea'.[8 9] Kalow and colleagues[10 11] unravelled the mystery and described several genetic abnormalities that give rise to atypical forms of BChE (also called pseudocholinesterase or plasma cholinesterase), the enzyme that hydrolyses succinylcholine. As such, suxemethonium or 'scoline' apnoea became one of the first well-characterized pharmacogenetic disorders.[12]

What the studies by Thomsen and colleagues[1 2] reveal about patients with atypical forms of BChE undergoing general anesthesia including succinylcholine or mivacurium is illuminating. However, we believe that their implications are far from esoteric and that they are profoundly informative in relation to patients who do not have BChE abnormalities or deficiency. Despite neuromuscular monitoring being risk free and entirely non-invasive, many anaesthetists continue to administer neuromuscular blocking agents without such monitoring. This suboptimal practice is associated with a high incidence (~40%) of at least mild postoperative weakness among surgical patients admitted to postoperative recovery areas.[3 5] By providing a model enriched for severe postoperative weakness, Thomsen and colleagues[1 2] force us to consider that many of our patients with postoperative weakness are likely to be experiencing distressing awareness on awakening, even if they do not remember such experiences. Likewise, many patients are likely to suffer preventable respiratory complications.

There are three possible mechanisms of protection with neuromuscular monitoring: (i) prevention of premature wakening; (ii) restriction of pharmacological neuromuscular blocking agent administration; and (iii) appropriate dosing of antagonist medication.[3 4] It is now well established that the sensation of paralysis is a key contributor to intraoperative awareness and the distress associated with awareness.[13] It therefore comes as no surprise that the sensation of paralysis after completion of the surgery is a cause of mental anguish, from which we must protect our patients. The most parsimonious approach to avoidance of distressing intraoperative or postoperative awareness is to limit or preferably avoid the administration of neuromuscular blocking agents (see Fig. 1). These drugs continue to enjoy gratuitous administration, possibly on the basis of perceived convenience rather than on the basis of surgical necessity. For example, to immobilize the heart potassium is required, whereas non-depolarizing neuromuscular blocking agents (fortunately) are not cardioplegic. Nevertheless, the majority of patients undergoing open cardiac procedures are subjected to pharmacological paralysis of all their skeletal muscles. We are gaining experience with a repertoire of invasive procedures where patients receive no neuromuscular blocking agents; examples include major spine surgeries, where patients are in the prone position for prolonged periods, and other invasive procedures, with the head fixed in a Mayfield frame.

When neuromuscular blocking agents are needed to facilitate surgery, it is important not to administer the competitive antagonist neostigmine before the return of four visible twitches in a train of four on a peripheral nerve stimulator in order to succeed reliably in reversing the pharmacologically induced weakness.[6 14] Neostigmine has a ceiling effect and will not prevent weakness if administered when a neuromuscular block is still profound, as revealed by a train-of-four ratio <0.4 at the adductor pollicis muscle following ulnar nerve stimulation.[6] Furthermore, neostigmine should be administered ~20 min before planned tracheal extubation to allow time for peak drug effect (see Fig. 1).[14] It is worth emphasizing that not all forms of neuromuscular monitoring are equal in terms of their reliability. With qualitative assessment (i.e. visual inspection or palpation), we are unable to distinguish between train-of-four ratios of 1 and 0.4.[6] Quantitative monitoring (e.g. acceleromyography, mechanomyography,

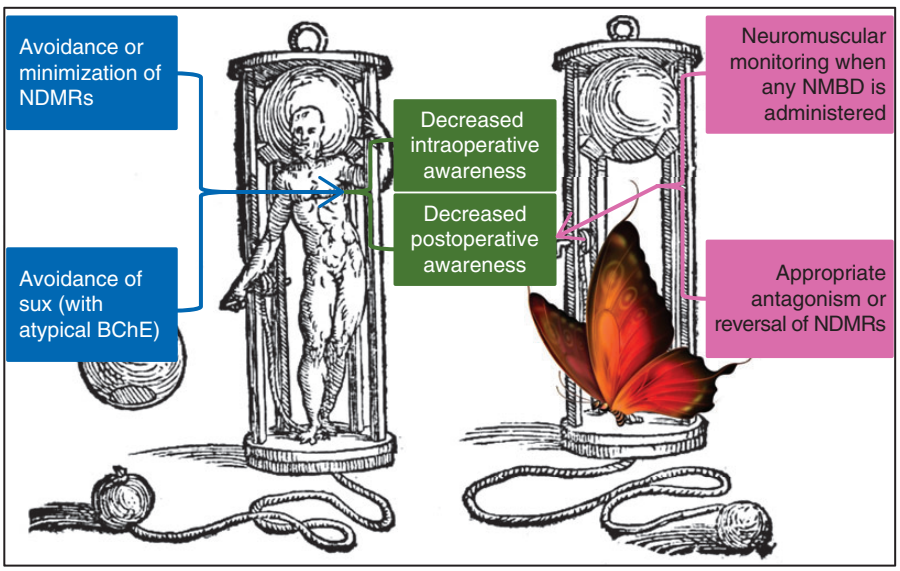

Fig 1 Evidence-based approaches to prevent intraoperative and postoperative awareness regarding the administration and monitoring of neuromuscular blocking agents. BChE, butyrylcholinesterase; NDMR, non-depolarizing neuromuscular blocking agent; NMBD, neuromuscular blocking drug; sux, succinylcholine. An early diving bell used by 16th century divers during salvage operations. http://commons.wikimedia.org/wiki/File:Diving_bell_noaa.jpg.

kinemyography, and electromyography) is reliable in excluding residual weakness after non-depolarizing or depolarizing neuromuscular blocking agents, if a baseline was established before succinylcholine administration.[6 15 16] Given that inhibitors of acetylcholinesterase (the enzyme that hydrolyses the neurotransmitter acetylcholine) can independently cause weakness through excessive cholinergic stimulation, a mismatch in dosing between neuromuscular blocking agents and the intended antagonist can result in weakness. Even the administration of a chemical antagonist of steroid neuromuscular blocking agents (i.e. sugammadex) might not prevent postoperative weakness.[17] When sugammadex is administered without neuromuscular monitoring, ~10% of patients still have a train-of-four ratio ≤0.9.[17]

A principle governing anaesthetic practice should be that if an inexpensive and non-invasive monitor is available for a physiological system that is pharmacologically perturbed, consideration should be given to incorporating such a monitor into routine clinical practice. Organ systems to which this principle could reasonably apply include the cardiovascular system (blood pressure, heart rate, and electrocardiogram); the respiratory system (respiratory rate, tidal volume, oximetry, and capnography); the thermoregulatory system (temperature); the central nervous system (electroencephalography); and the neuromuscular system (neuromuscular monitoring). It is ironic that the very targets that are directly affected by anaesthetic and neuromuscular blocking agents (i.e. the brain and the neuromuscular junction) are the very organs that are currently not monitored routinely during general anaesthesia. Unlike the data pertaining to the monitoring of any other organ system, the data are by now compelling that withholding neuromuscular monitoring from our patients is associated with morbidity and distress.[5 14] For regulatory organizations, it is time to get off the fence and to mandate neuromuscular monitoring as the standard of care whenever depolarizing and non-depolarizing neuromuscular blocking agents are administered in the operating theatre or in the intensive care unit (see Fig. 1).

When our patients wake up weak and struggling for breath, the experience could feel like being pinioned in the cocoon of a diving bell, deprived of oxygen, and able to register discomfort only with desperate, twitching gestures. We, the anaesthetists must learn from the harsh experiences of patients with atypical BChE and apply uniform principles in our practice to ensure that our patients always emerge from general anaesthesia like unencumbered butterflies.

Declaration of interest

M.S.A. is an member of the Associate Editorial Board of the *BJA*.

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ARTICLE

ARTICLE

Awareness during emergence from anaesthesia: significance of neuromuscular monitoring in patients with butyrylcholinesterase deficiency†

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Abstract

Background: Butyrylcholinesterase deficiency can result in prolonged paralysis after administration of succinylcholine or mivacurium. We conducted an interview study to assess whether patients with butyrylcholinesterase deficiency were more likely to have experienced awareness during emergence from anaesthesia if neuromuscular monitoring had not been applied.
Methods: Patients referred during 2004–2012 were included. Data on the use of neuromuscular monitoring were available from a previous study. Interviews, conducted by telephone, included questions about awareness and screening for post-traumatic stress disorder. Reports of panic, hopelessness, suffocation, or a feeling of being dead or dying resulted in the experience being classified further as distressful. Patients were categorized as aware or unaware by investigators blinded to use of neuromuscular monitoring.
Results: Ninety-five patients were eligible to be interviewed. Of the 70 patients interviewed, 35 (50%) were aware while paralysed during emergence. Of these, 28 (80%) were not monitored with a nerve stimulator when awakened, compared with 17 (49%) of the 35 unaware patients (P=0.012, Fisher's exact test). Thirty (86%) aware patients reported distress compared with seven (20%) unaware patients (P<0.001). The aware patients scored higher in screening for post-traumatic stress disorder (P=0.006, Mann–Whitney U-test).
Conclusions: Butyrylcholinesterase deficiency is a major risk factor for distressing awareness during emergence. Lack of neuromuscular monitoring increases the risk significantly. Neuromuscular monitoring should be applied even when using short-acting neuromuscular blocking agents.

Key words: anaesthesia awareness; butyrylcholinesterase deficiency; neuromuscular block; neuromuscular monitoring

Editor's key points

- Prolonged paralysis after succinylcholine or mivacurium occurs in patients with butyrylcholinesterase deficiency.
- Patients suspected of butyrylcholinesterase deficiency were interviewed to determine their experience of awareness of paralysis during emergence from anaesthesia.
- Of the patients interviewed, 50% reported paralysis, and these patients were less likely to have had neuromuscular function monitoring.

Patients with butyrylcholinesterase (BChE) deficiency could be at risk of experiencing severe residual neuromuscular block because the enzyme deficiency causes prolonged duration of action of the short-acting neuromuscular blocking agents succinylcholine and mivacurium.[1 2] Butyrylcholinesterase deficiency may be suspected if neuromuscular monitoring shows no response to nerve stimulation when anaesthesia is about to be terminated. If neuromuscular monitoring is not applied, paralysis and apnoea upon discontinuation of anaesthesia may lead to suspicion of BChE deficiency.[3 4]

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The recently published 5th National Audit Project (NAP5) on accidental awareness in general anaesthesia revealed that the experience of emerging from anaesthesia with residual neuromuscular block was interpreted by many patients as anaesthesia awareness.[5] Failure to monitor the degree of neuromuscular block with a nerve stimulator was judged causal or contributory in the majority of these instances.

The Danish Cholinesterase Research Unit (DCRU) receives referrals of patients suspected of BChE deficiency.[6] In a DCRU registry study (Thomsen and colleagues),[7] we found that application of neuromuscular monitoring was associated with lower risk of premature awakening in patients suspected of BChE deficiency. However, it has never been investigated whether patients with BChE deficiency are genuinely at increased risk of awareness. In the present interview study, we investigated whether patients suspected of BChE deficiency were more likely to have experienced awareness during emergence from anaesthesia if they were not monitored with a nerve stimulator.

Methods

The Committees on Health Research Ethics in Denmark confirmed that the study could be initiated without approval (H-4-2013-164). The Danish Data Protection Agency (HEH-2014-003/02597) approved the study. The DCRU is a clinical database registered with the Danish Data Protection Agency.

Eligibility

We included patients referred to the DCRU from January 2004 to May 2012. Data on the use of neuromuscular monitoring were available from an earlier study. In that study, two groups were defined: patients monitored with a nerve stimulator from the beginning of anaesthesia (monitored group), and patients not monitored at all (unmonitored group). Patients for whom a nerve stimulator was applied only when residual neuromuscular block was suspected were also included in the unmonitored group because this was considered inappropriate use of neuromuscular monitoring. Patients were excluded from the present study if they were <18 yr old at the time of the interview, <15 yr old at the time of the procedure leading to referral to the DCRU, or were unable to complete the interview because of mental impairment, non-Danish speaking, or death. Patients who declined participation or who could not be contacted were also excluded.

Interviews

We designed an interview guide consisting of multiple choice and open-ended questions related to the perioperative experience (Table 1). The interview guide was based on experiences reported in studies of awareness in anaesthesia.[8–10] A modified Brice interview was included to differentiate between intraoperative awareness and awareness during emergence from anaesthesia.[11] As anaesthesia awareness can lead to post-traumatic stress disorder (PTSD),[13] we also included the PTSD checklist specific version (PCL-S)[12] to screen for long-term psychological sequelae. The checklist consists of 17 items in four categories of PTSD symptoms: re-experiencing, avoidance, numbing, and hyperarousal. Each item is scored from 1 'not at all' to 5 'extremely', resulting in a total score between 17 and 85. We chose a cut-off value of 44 as indicative of possible PTSD as proposed by Blanchard and colleagues.[14] The choice of cut-off value of the PCL-S has an effect on the specificity and the sensitivity of the test as a screening tool for PTSD. Also, the optimal cut-off value can be found only when the true prevalence of PTSD in the population is known.[15] Patients were asked to participate in the interview study by letter. A reminder was sent to non-responders after 2 months. Three investigators (J.L.T., K.Z.E., and M.N.D.) conducted the interviews by telephone. Before this, the investigators discussed the interview guide extensively to ensure that interviews were conducted in the same manner. To reduce interviewer bias, the investigators were blinded to all clinical information except the following: the indication for the procedure, hospital, date of surgery, and the patient's age at the time of the procedure. Patients were informed that the purpose of the study was to describe their perioperative experience, but not about the intended examination of the association between neuromuscular monitoring and awareness during emergence from anaesthesia. Replies were typed directly in an electronic form containing the interview guide. Patients reporting psychological sequelae were advised to contact their general practitioner.

Assessment and classification

Two investigators (J.L.T. and M.R.G.) reviewed the responses to assess whether the patients had been aware while paralysed during emergence from anaesthesia. Patients reporting actual paralysis, e.g. inability to open their eyes, move, breathe, or speak while still in the operating room (OR), were classified as aware. Patients with an uneventful emergence from anaesthesia and no report of paralysis constituted the unaware group. Patients reporting 'feeling heavy', but not paralysed, or for whom it could not be determined if the reported incident took place in the OR or in the intensive care unit (ICU) were classified as 'possible', and were included in the aware group. Patients who had experienced paralysis after leaving the OR (i.e. in the ICU) were classified as paralysed in the ICU. Hence, a patient could be classified as unaware (in the OR), but paralysed in the ICU. Finally, the assessors judged whether the postoperative experience as a whole was described as distressing, according to the Michigan awareness scale.[16] Among others, reports of panic, hopelessness, suffocation, or a feeling of being dead or dying (Table 1) resulted in the experience being classified as distressful. Disagreements were settled by discussion. The assessors were blinded to clinical data (i.e. the use of neuromuscular monitoring).

Outcomes

The primary outcome was awareness during emergence from anaesthesia. Secondary outcomes were paralysis in the ICU, experience reported as distressing, and total PCL-S score. Patients with pre-existing anxiety, depression, or PTSD were excluded from the analysis of the PCL-S score.

Statistical analysis

Categorical data were compared using Fisher's exact test. The correlation between use of neuromuscular monitoring and awareness during emergence from anaesthesia was calculated using logistic regression and reported as odds ratio with 95% confidence interval (CI). Possible confounders were tested for statistical significance and, if found significant, included in the analysis, giving an adjusted odds ratio. The PCL-S scores were compared using the Mann–Whitney *U*-test. Analyses were done in SPSS (version 19.0; SPSS Inc., Chicago, IL, USA) and R (version 3.1.0; R Foundation for Statistical Computing, Vienna, Austria). A value of $P<0.05$ was considered statistically significant.

Table 1 Interview guide. Based on experiences reported in awareness studies,[8–10] the modified Brice interview,[11] and the post-traumatic stress disorder (PTSD) checklist specific version (PCL-S)[12]

Introduction to the participants:

You were referred to the Danish Cholinesterase Research Unit because you are suspected to be genetically disposed to prolonged duration of action of a neuromuscular relaxant administered during your anaesthetic. Most of the following questions are multiple choice, while some are open ended. Unless stated otherwise, options for answering are 'yes', 'no', and 'cannot remember'. Most questions are followed by an option to comment.

Introduction

How was your overall experience of the procedure and anaesthetic?
(a) Very good
(b) Good
(c) Neutral
(d) Bad
(e) Very bad

Modified Brice interview

What is the last thing you remember from before going to sleep?
What is the first thing you remember from after waking up?
Do you remember anything from the period between going to sleep and waking up?
Did you dream during your procedure?
What was the worst part?
(a) Before arrival to the operating room
(b) In the operating room, before anaesthesia was induced
(c) During the procedure
(d) In the operating room at emergence from anaesthesia
(e) In the postanaesthesia care unit
(f) After discharge from the postanaesthesia care unit
(g) No unpleasant experience at all

Emergence from anaesthesia

How was your experience of waking up?
(a) Very pleasant
(b) Pleasant
(c) Neutral
(d) Unpleasant
(e) Very unpleasant
(f) Cannot remember

What caused you to experience the awakening in such a manner?

Did you try to move?
Were you able to move?
Did you understand right away what was happening?
Did you experience (yes or no to each item):
(a) Feeling safe
(b) Being comforted verbally
(c) Hearing sounds
(d) Hearing voices
(e) Visual impressions
(f) Touch, without pain
(g) Fear of pain
(h) Light pain
(i) Severe pain
(j) Feeling unsafe
(k) Feeling panic
(l) Wanting to ask for help, but not being able to
(m) A feeling of hopelessness
(n) Suffocation
(o) Muscle weakness
(p) Paralysis
(q) Feeling that you were dead or dying
(r) Feeling that you were being betrayed by your physician or nurse anaesthetist, or both
(s) None of the above
(t) Other, elaborate

PTSD Checklist Specific Version (PCL-S)

Continued

Table 1 *Continued*

In the following, 17 problems and complaints that people sometimes have in response to stressful life experiences will be mentioned. In this case, the stressful experience refers to the procedure and anaesthetic. Please listen to each one carefully, and then give your answer to indicate how much you have been bothered by that problem in the past month. For each question, please choose the best-suiting answer: not at all, a little bit, moderately, quite a bit, and extremely.

In the past month, to which degree have you been bothered by:

1. Repeated, disturbing memories, thoughts, or images of the stressful experience?
2. Repeated, disturbing dreams of the stressful experience?
3. Suddenly acting or feeling as if the stressful experience were happening again (as if you were reliving it)?
4. Feeling very upset when something reminded you of the stressful experience?
5. Having physical reactions (e.g. heart pounding, trouble breathing, sweating) when something reminded you of the stressful experience?
6. Avoiding thinking about or talking about the stressful experience or avoiding having feelings related to it?
7. Avoiding activities or situations—including avoiding anaesthesia or going to the hospital—because they reminded you of the stressful experience?
8. Trouble remembering important parts of the stressful experience?
9. Loss of interest in activities that you used to enjoy?
10. Feeling distant or cut off from other people?
11. Feeling emotionally numb or being unable to have loving feelings for those close to you?
12. Feeling as if your future somehow will be cut short?
13. Trouble falling or staying asleep?
14. Feeling irritable or having angry outbursts?
15. Having difficulty concentrating?
16. Being 'super alert' or watchful or on guard?
17. Feeling jumpy or easily startled?

Were any of the five lastly mentioned problems present before the stressful experience?

Remark: each item is scored as 1 (not at all), 2 (a little bit), 3 (moderately), 4 (quite a bit), or 5 (extremely). A total symptom severity score (range=17–85) is obtained by summing the scores from each of the 17 items.

Concluding questions

Did you receive any kind of professional counselling because of your experience?

Did you suffer from any diagnosed psychiatric illness before the experienced event or have you been diagnosed after the experience?

Do you have any supplementary information that you find relevant for this study?

A sample size calculation was not conducted before initiation of the study.

Results

A total of 127 patients were eligible, including the 123 patients analysed in the companion paper.[7] An additional four patients who were excluded from the other study because of missing information of the primary outcome were also included. Of 95 - patients eligible for interview, contact could not be obtained in 24 instances and one patient declined to participate, resulting in 70 interviewed patients (Fig. 1).

Interviews were conducted from December 2012 to March 2013. Patient characteristics and perioperative data for the aware and unaware groups are shown in Table 2. The duration of interview was mean 29 min (range 13–68) and 22 min (range 10–46) in the aware and unaware group, respectively. Interviews were conducted with the aware and unaware patients 4 yr (range 1–9) and 5 yr (range 1–9) after the anaesthesia event that led to referral to the DCRU. The cause for BChE deficiency was homozygous mutations in the butyrylcholinesterase (*BCHE*) gene in 51 (73%) patients and heterozygous mutations in 10 (14%) patients (Table 2). Five (7%) patients had a normal genotype with medication or conditions that decrease BChE activity, while four (6%) had a normal genotype with non-BChE-related explanations for the events that led to referral.

Awareness during emergence from anaesthesia and paralysis in the intensive care unit

A total of 31 (44%) of the 70 patients interviewed had experienced awareness during emergence from anaesthesia. An additional four patients (6%) were classified as 'possible' and were included in the aware group. Of the 35 patients in the aware group, 28 (80%) were not monitored with a nerve stimulator when anaesthesia was terminated, compared with 17 (49%) of 35 in the unaware group (P=0.012). Neuromuscular monitoring reduced the risk of awareness during emergence from anaesthesia [odds ratio 0.24 (95% CI 0.08–0.68), P=0.008]. Possible confounders tested for significance included the following: sex, ASA physical status, age, neuromuscular blocking agent administered (succinylcholine *vs* mivacurium or combinations), genotype (homozygous mutations *vs* others), and time since the procedure. Only age proved statistically significant [odds ratio 0.97 (95% CI 0.94–0.998), P=0.036] and was included in the analysis, resulting in an adjusted odds ratio of 0.23 (95% CI 0.08–0.68; P=0.008).

Upon completion of the study, we grouped patients according to reported experience, use of neuromuscular monitoring, and cause of prolonged neuromuscular block. Patients representative of these groups are reported in Table 3. Six (17%) patients in the aware group also reported being paralysed in the ICU after leaving the OR (Table 3, section B). Of the unaware patients, nine (26%) reported being paralysed in the ICU, but did not recall anything from the OR (Table 3, section C). The unaware patients

typically remembered nothing at all from the OR (Table 3, sections D and G). Seven patients experienced awareness during emergence from anaesthesia despite the use of neuromuscular monitoring (Table 3, section F). In five of these patients, neuromuscular monitoring was applied but apparently malfunctioning, or results were disregarded. In the remaining two patients, no problems with the nerve stimulator were reported in the anaesthesia records. While patients homozygous for *BCHE* mutations accounted for the most distressing instances of awareness during emergence from anaesthesia, six patients with heterozygous mutations or normal genotype with acquired BChE deficiency also reported being paralysed in the OR (Table 2 and Table 3, sections H and I).

Distress

The experience was assessed to be distressing in 30 (86%) of the aware patients and seven (20%) of the unaware patients ($P<0.001$). Of the five patients in the aware group reporting no distress, two had experienced the event as in a dream, one was half-asleep when realizing he was paralysed, one was conscious for only a very short time, and one described how the anaesthesia personnel calmly explained that the paralysis was only temporary (Table 3, section E). Of the seven unaware patients reporting distress, six had experienced paralysis in the ICU, explaining their distress (Table 3, section C).

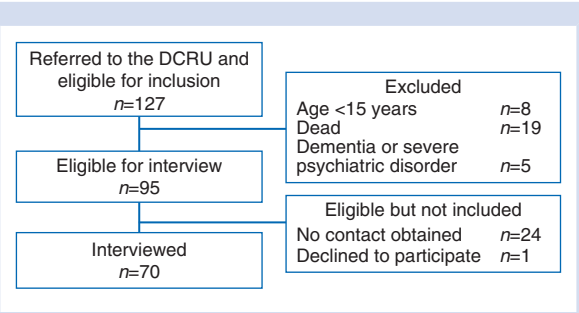

Fig 1 Study flow. DCRU, Danish Cholinesterase Research Unit.

Screening for post-traumatic stress disorder

In screening for PTSD, three patients were excluded because of a psychiatric condition diagnosed before the procedure: two with PTSD (one in the aware group, PCL-S score 62, one in the unaware group, PCL-S score 56) and one with anxiety and depression (unaware group, PCL-S score 72). This information was revealed at the end of the interview (Table 1). The median PCL-S scores in the 34 aware and 33 unaware patients were 19 (range 17–51) and 17 (range 17–35), respectively ($P=0.023$). One patient in the aware group had a PCL-S score of 51, indicating possible PTSD (Table 3, patient 2).

Discussion

Our study revealed that 50% of patients referred to the DCRU because of suspected BChE deficiency had experienced awareness during emergence from anaesthesia, thereby establishing BChE deficiency as a major risk factor for awareness. Aware patients were not monitored with a nerve stimulator in 80% of instances, or neuromuscular monitoring was applied only when BChE deficiency was suspected, which was after a failed attempt to awaken the patient. Furthermore, patients who had experienced awareness during emergence from anaesthesia scored higher in screening for PTSD.

Table 2 Characteristics of the 70 interviewed patients with and without awareness during emergence from anaesthesia. Data are mean (range) or number of patients (percentage). Aware, patients who experienced awareness during emergence from anaesthesia; BChE, butyrylcholinesterase enzyme; *BCHE*, butyrylcholinesterase gene; Unaware, patients who did not experience awareness during emergence from anaesthesia

	Aware (*n*=35)	Unaware (*n*=35)
Patient		
Sex (male:female)	13:22	19:16
Age at the procedure	41 (16–69)	50 (18–86)
Weight (kg)	82 (48–150)	78 (44–130)
Height (cm)	174 (156–194)	173 (158–198)
ASA physical status (I/II/III)	19/13/3	16/13/6
Procedure priority		
Urgent	16 (46%)	21 (60%)
Elective	17 (48%)	11 (31%)
Unknown	2 (6%)	3 (9%)
Neuromuscular blocking agent administered		
Succinylcholine	23 (66%)	20 (57%)
Mivacurium	6 (17%)	10 (28%)
Succinylcholine and mivacurium	2 (6%)	3 (9%)
Succinylcholine and other non-depolarizing neuromuscular blocking agent	4 (11%)	2 (6%)
Cause of prolonged duration of action of neuromuscular blocking agent		
Homozygous for *BCHE* mutations	27 (77%)	24 (69%)
Heterozygous for *BCHE* mutation with or without concurrent medication or conditions that decrease BChE activity	3 (9%)	7 (20%)
Normal genotype with medication or conditions that decrease BChE activity	3 (9%)	2 (6%)
Normal genotype with non-BChE-related explanation for the events that led to referral, such as overdosing of neuromuscular blocking agents	2 (5%)	2 (5%)

Table 3 Patients of special relevance. BChE, butyrylcholinesterase enzyme; *BCHE*, butyrylcholinesterase gene; DCRU, Danish Cholinesterase Research Unit; Heterozygote, heterozygous for *BCHE* mutation with or without medication or conditions decreasing BChE activity; Homozygote, homozygous for *BCHE* mutations; ICU, intensive care unit; OR, operating room; PCL-S, post-traumatic stress disorder checklist; TOF, train of four

Patient no.	Sex, age (yr)	Procedure	Cause of BChE deficiency	Reported experience of awareness during emergence from anaesthesia	PCL-S score	Neuromuscular monitoring	Clinical data from anaesthesia records and the DCRU
Section A: aware, unmonitored							
1	F, 47	Arthroscopy	Homozygote	Woke up in the OR and felt fine, except breathing took an effort. Received neostigmine (the patient is a nurse), which eased her breathing initially, but as they moved her to the hospital bed, her tongue fell back, choking her. Panicked, but could not advise the staff that she was awake. Pulse oximetry was applied. Received neostigmine again, this time resulting in complete paralysis. Was awake while being bag mask ventilated. Follow-up: received counselling from a psychologist.	23	Applied after suspicion of BChE deficiency	Anaesthesia discontinued 75 min after succinylcholine administration. Trachea extubated at 90 min. Received neostigmine at 95 and 130 min. Bag mask ventilated. Tracheally reintubated at 130 min with a second dose of succinylcholine. Neuromuscular monitoring applied after reintubation.
2	F, 28	Diagnostic laparoscopy	Homozygote	Nurse telling her to breathe or try to move. Heard and understood everything, but unable to follow instructions. Nurse said 'we have to put her back to sleep'. Woke up abruptly, and the tracheal tube was removed. Was told that she almost died. Follow-up: saw a psychologist 6 months later.	51	Applied after suspicion of BChE deficiency	Anaesthesia discontinued 45 min after succinylcholine administration. Return of spontaneous respiration with tidal volumes of 100 ml at 80 min. Resedated.
3	F, 39	Nasal surgery	Homozygote	Was thinking that something was very wrong. Could hear the staff talking, but could not see anything or move. Tried to move her finger to give a signal that she was awake. Heard someone say 'she is waking up'. The staff did not panic, but she could tell that it was an unusual situation. Took a long time before they reassured her that everything was going to be fine. Felt loss of control and wanted to scream.	35	Not applied	Anaesthesia discontinued 35 min after succinylcholine administration. The patient confirmed to the anaesthetist that she was awake by lifting a finger and squinting her eyes. Resedated.
4	M, 62	Unknown procedure	Homozygote	Could not move his body or eyes. Was able to breathe, but it took an effort. Someone said 'he is awake'. Awake for about 5 min. Fell asleep again. Follow-up: was offered psychologist counselling, but did not feel the need.	17	Applied after suspicion of BChE deficiency	Anaesthesia discontinued 30 min after succinylcholine administration. Resedated. TOF count 0 after attempted awakening.
5	M, 29	Oesophagoscopy	Homozygote	Woke up paralysed. Heard voices. Felt he was choking. Could not tell the staff that he was awake. Did not understand what was happening. Follow-up: received a phone number in case he	17	Not applied	Anaesthesia discontinued 23 min after succinylcholine administration. Received naloxone on suspicion of opioid overdose. Resedated.

Continued

Table 3 *Continued*

Patient no.	Sex, age (yr)	Procedure	Cause of BChE deficiency	Reported experience of awareness during emergence from anaesthesia	PCL-S score	Neuromuscular monitoring	Clinical data from anaesthesia records and the DCRU
				needed to talk about it afterwards, but did not need to.			
Section B: aware postoperatively and experienced paralysis in the ICU							
6	F, 33	Laparoscopic cholecystectomy	Homozygote	Saw a doctor opening her eye and telling her to wake up. One of the staff said something like 'let us give her another 30 min'. Later, she heard a nurse complaining about having to stay late because of her. When transferred to the ICU, still tracheally intubated and unable to move, they addressed her, saying that everything was fine. In the following hours, every time they opened her eyes to check on her, she could track the time on a clock hanging on the opposite wall. Drifted in and out of consciousness. Follow-up: consulted a psychologist.	34	Applied after suspicion of BChE deficiency	Anaesthesia discontinued 50 min after mivacurium administration. Heart rate increased to 140 beats min^{-1}. Resedated after 10 min. Return of spontaneous respiration at 330 min, sufficient at 365 min.
7	F, 29	Appendectomy	Homozygote	Heard someone saying 'you can wake up now', but could not open her eyes. Was thinking 'I am dying'. More staff entered the OR; they suspected prolonged action of the medicine. Later, when she woke up and opened her eyes, the tracheal tube was quickly removed. Fully conscious while someone lifted her jaw to help her breathe for ~2 h. Tried hard to move just a hand or a finger. Follow-up: was offered to see a psychologist, but refrained. Had nightmares about the incident for 2–3 months.	17	Applied after suspicion of BChE deficiency	Anaesthesia discontinued 45 min after succinylcholine administration. Received naloxone after another 20 min. Resedated. TOF ratio measured to be 0.45. Trachea extubated at 150 min, but required jaw thrust, bag mask ventilation and suctioning.
Section C: unaware in the OR, but experienced paralysis in the ICU							
8	F, 58	Gastroscopy	Homozygote	Nurse in the ICU asked how she felt. Could not breathe, was only able to nod her head. Tracheal tube in her mouth and a stinging sensation in one hand. Follow-up: reported a very active gag reflex after the incident.	30	Not applied	Anaesthesia discontinued 30 min after succinylcholine administration. Shallow spontaneous respiration at end-tidal sevoflurane of 0.1%. Blood pressure of 240/130 mm Hg. Resedated and transferred for a CT scan.
9	M, 68	Herniotomy	Homozygote	Felt as if everything but his brain was anaesthetized. Experienced going towards a bright light after someone said 'he is not breathing'. Was patted hard on the cheek and told to wake up. Could only see when they opened his eyes.	17	Not applied	Anaesthesia discontinued 25 min after succinylcholine administration. Resedated after 20 min. Manually ventilated for 90 min. Return of spontaneous respiration after more than 150 min.
Section D: unaware, monitored							
10	F, 35		Homozygote		17	Applied	

		Gynaecological surgery		A caring nurse telling her that she was in the ICU. Relieved. Did not realize that she had slept about 3 h longer than planned.			TOF count 0 measured 75 min after mivacurium administration. Change to a different nerve stimulator and stimulus current increased. BChE deficiency suspected. Transferred to ICU.
11	M, 21	Appendectomy	Homozygote	Woke up thirsty and hungry in the ICU. Follow-up: the staff told him that he took a long time to emerge from anaesthesia.	17	Applied	Anaesthesia discontinued 150 min after succinylcholine administration. TOF ratio 0.9 at 140 min.
12	M, 24	Appendectomy	Homozygote	Woke up nauseated and with a headache in the ICU. Very tired, felt like a hangover.	17	Applied	Anaesthesia discontinued 170 min after succinylcholine administration. TOF count 4 at 75 min. TOF ratio 0.9 at 180 min.
Section E: aware without distress							
13	F, 53	Phlebectomy	Homozygote	Saw lot of people standing over her and shouting her name, then fell back to sleep. Woke up in a different hospital than where she had surgery done. Strange experience, but felt no distress.	17	Applied after suspicion of BChE deficiency	Anaesthesia discontinued 45 min after succinylcholine administration. Awakened and resedated twice.
14	M, 64	Cholangiopancreato-graphy	Homozygote	Someone talking to him, unable to reply. Was half-asleep, but understood that the anaesthetic did not work as supposed.	23	Applied after suspicion of BChE deficiency	Anaesthesia discontinued 65 min after succinylcholine administration. Neuromuscular monitoring applied at 80 min, showing TOF count 1. Resedated and transferred to ICU.
Section F: aware, monitored							
15	M, 29	Endoscopy of jejunal pouch	Homozygote	Could not open his eyes or breathe. Realized he was in the OR and that something was totally wrong. Heard a slight panic around him. Follow-up: was told that he had been awakened though the nerve stimulator had shown no response. Felt betrayed.	39	Applied	Electrodes on nerve stimulator replaced. Anaesthesia discontinued 15 min after succinylcholine administration. Received neostigmine.
16	F, 21	Appendectomy	Homozygote	Heard people yelling at her to lift her head. Tried to, but could not. Realized she had a tube in her mouth; found it odd. Quickly fell asleep again. Woke up under a heating blanket in the ICU. It was not unpleasant waking up the second time.	21	Applied	Changed to a different nerve stimulator and electrodes changed. Nurse anaesthetist and junior anaesthesiologist suspected BChE deficiency, but the anaesthesiologist in charge thought it to be caused by equipment malfunctioning. Anaesthesia discontinued 65 min after succinylcholine administration. Resedated.
Section G: unaware, unmonitored							
17	F, 30	Exploratory laparotomy	Homozygote	Does not remember anything from the OR. Woke up in the ICU, still tracheally intubated. The tube was removed promptly. Did not understand why she was in the ICU. Saw the clock and realized	17	Applied after suspicion of BChE deficiency	Anaesthesia discontinued 30 min after succinylcholine administration.

Continued

Table 3 *Continued*

Patient no.	Sex, age (yr)	Procedure	Cause of BChE deficiency	Reported experience of awareness during emergence from anaesthesia	PCL-S score	Neuromuscular monitoring	Clinical data from anaesthesia records and the DCRU
				that quite a while had passed. A doctor explained what had happened, taking it very seriously.			
18	M, 86	Revision of crural ulcer	Homozygote	Woke up in the ICU, still tracheally intubated. Recalled nothing from the OR.	19	Applied after suspicion of BChE deficiency	Anaesthesia discontinued 30 min after succinylcholine administration. Trachea extubated at 125 min. Ventilated with a laryngeal mask airway for 40 min, then tracheally reintubated.
Section H: patients heterozygous for *BCHE* mutation							
19	F, 29	Surgery for postpartum haemorrhage	Heterozygote and low BChE activity attributable to recent pregnancy	ICU nurse asked her to lift her arms or legs, but she could not. Unable to speak, could only make guttural noises.	17	Not applied	Anaesthesia discontinued 10 min after succinylcholine administration. Not resedated. Unable to move extremities at 30 min. At 90 min the patient was awake and able to respond and move extremities.
20	F, 19	Uterine evacuation	Heterozygote and oral contraceptive	Could not move or breathe. Sensed people close to her, like shadows, but could not open her eyes. A frantic activity in the room. Realized she could not breathe, panicked, and then fell asleep.	17	Applied after suspicion of BChE deficiency	Anaesthesia discontinued 5 min after succinylcholine administration. Not resedated. Return of spontaneous respiration at 20 min. Low BChE activity.
21	F, 22	Nasal surgery	Heterozygote and oral contraceptive	Her body was not awake. Could not open eyes or move, but heard everything that was being said. They repeated the same sentence over and over, until they realized that something was wrong. Fell back to sleep.	17	Applied after suspicion of BChE deficiency	Anaesthesia discontinued 45 min after mivacurium administration. Tracheal extubation at 55 min. Laboured breathing. Resedated. Neuromuscular monitoring applied, showing TOF ratio 0.2. Bag mask ventilated.
22	F, 33	Arthroscopy of jaw	Heterozygote and sevoflurane anaesthesia	Woke up in the OR. Could not speak or move, but heard people around her. Realized that something had gone wrong. Awake for only a short time.	17	Not applied	Anaesthesia discontinued 45 min after mivacurium administration. Resedated.
				Section I: aware, wild-type *BCHE* with low BChE activity			
23	M, 41	Electrical cardioversion	Wild-type with systemic disease and medication affecting BChE activity	Could move only his eyes; otherwise, completely paralysed. Tried to scream, but nothing happened. Could not breathe; thought he was permanently paralysed. He was in panic for 15–20 min. Still with a tube in his mouth, he slowly regained muscle strength and could move his fingers. Follow-up: saw a psychologist, but primarily because of his illness.	25	Not applied	Very low BChE activity. Lung transplanted. Succinylcholine dose unknown. Referral form: 15 min to return of spontaneous respiration, 25 min to sufficient respiration.

To our knowledge, no study has examined the subjective experience of patients with BChE deficiency systematically. Numerous case reports describe patients with prolonged neuromuscular block from succinylcholine or mivacurium. In some of these, patients may have been conscious while paralysed,[3 17 18] but the patient's own experience is rarely described. Combining data from the DCRU with structured interviews provided a unique opportunity to describe the point of view of patients with BChE deficiency. Our study showed that patients either homozygous or heterozygous for *BCHE* mutations can experience postoperative paralysis, resulting in awareness. Homozygosity of the clinically most important *BCHE* mutation (the atypical variant A) occurs with a frequency of one in 3000 in Caucasians and results in prolonged duration of action of 2–3 h after succinylcholine 1 mg kg^{-1} i.v. However, one in five people carry the most common low-activity variant, the K-variant.[19] Patients heterozygous or homozygous for the K-variant have 30% prolonged neuromuscular block,[20] which can also be clinically relevant for short procedures, such as electroconvulsive therapy or reduction of hip dislocation.[21] This indicates that awareness during emergence from anaesthesia could be a common but underreported problem.

As in NAP5,[22] many patients in the present study found it very distressing suddenly to be awake while paralysed; some even believed that they were dead or dying. Others felt no distress because they were confident that the paralysis was only temporary. Likewise, Pilgram and colleagues[4] reported on a patient who experienced no fear or helplessness because she had faith in the anaesthesiologist, who kept her calm through the 30 min that passed before neuromuscular monitoring was applied and the condition was recognized. Also, completely paralysed well-informed volunteers reported no distress as long as they were not hypercapnic.[23] Unlike the patients in our study, the volunteers had practised the procedure beforehand and were even able to communicate through hand gestures, probably making it much less traumatic. Our findings support that informing and calming a patient who is unexpectedly conscious while paralysed is important to prevent distress.

Paralysis in the intensive care unit

Some patients were conscious while paralysed, not only at the primary awakening attempt in the OR, but also when transferred to the ICU, after BChE deficiency was suspected. They may have been insufficiently sedated after BChE deficiency was recognized, or they may have been awakened a second time after arrival to the ICU before regaining full neuromuscular function. Most patients receiving intensive care are only sedated lightly. In contrast, patients with newly recognized BChE deficiency may be completely paralysed for hours without being able to communicate or understand the situation. This emphasizes the importance of sufficient sedation until neuromuscular function has fully recovered.

Long-term psychological consequences

Awareness has not been described systematically in patients with BChE deficiency before, nor have its long-term psychological consequences. Intraoperative awareness is reported to result in PTSD in 0–71% of cases.[12] We screened one patient positive for PTSD in the aware group and none in the unaware group. However, our study is too small to draw any conclusions about the true incidence of PTSD in this population. Our finding of a small but statistically significant difference of two points in PCL-S total score between patients with and without neuromuscular monitoring may be of questionable clinical significance in itself. Even so, awareness during emergence from anaesthesia must be considered a serious complication to anaesthesia based on the primary outcome alone. Future studies may reveal whether patients with BChE deficiency are indeed at risk of developing PTSD if aware while paralysed.

Significance of neuromuscular monitoring

Many of the distressing experiences reported could have been avoided by careful application of quantitative neuromuscular monitoring before awakening, reassuring the patient if awakened prematurely, and by sufficient sedation until full recovery of neuromuscular function. Experts in the field have recommended the use of quantitative neuromuscular monitoring whenever a non-depolarizing neuromuscular blocking agent is administered.[24 25] This recommendation should be applied to all neuromuscular blocking agents, including succinylcholine, because the BChE activity of an individual patient is rarely known before the procedure. In order to enable anaesthetists to comply with such recommendations, there is a need for education in neuromuscular monitoring and rational management of the neuromuscular block.

Limitations

The study has some limitations. The questionnaire developed was not validated, although the PCL-S screening instrument has been validated in Norwegian, a language very similar to Danish.[26] Furthermore, the PCL-S should be used cautiously when screening is not followed by a more thorough and time-consuming standardized diagnostic interview.[15] The questionnaire could have been tested on a group of surgical patients without BChE deficiency, in order to determine the contribution of BChE deficiency to the postoperative experience. The delay between procedure and interview may have caused underreporting of awareness during emergence from anaesthesia, perhaps especially in patients without distress. The assessors of the experiences are not experts in awareness. However, in contrast to intraoperative awareness, the assessor did not judge the authenticity of the reported experiences as is done when assessing intraoperative awareness, but merely if paralysis was reported. The 25 patients who were eligible but could not be interviewed may have affected our results. Acknowledging these limitations, we believe that our findings are relevant, not only to patients with BChE deficiency, but also to any patient receiving a neuromuscular blocking agent.

Conclusion

In conclusion, we found that 50% of patients suspected of BChE deficiency had experienced awareness during emergence from anaesthesia. Neuromuscular monitoring was not applied before awakening in the majority of aware patients, and it seems to be the tool for preventing awareness during emergence from anaesthesia. Hence, neuromuscular monitoring should be applied even when using short-acting BCHE-metabolized neuromuscular blocking agents.

Authors' contributions

J.L.T.: study conception and design, conduct of interviews, analysis and interpretation of results, writing of first draft of the paper. C.V.N.: study conception and design. K.Z.E. and M.N. D.: conduct of interviews. M.R.G.: study conception and design, analysis and interpretation of results. All authors have approved

the final manuscript for publication and agreed to be accountable for all aspects of the work.

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Declaration of interest

J.L.T.; C.V.N.; K.Z.E.; M.N.D.; M.R.G.; no interest declared. M.R.G. has received payment and travel funding for lectures from MSD, and has received funding to perform clinical studies from MSD.

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