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CLINICAL REPORT

Risk of aspiration during anesthesia in patients with congenital insensitivity to pain with anhidrosis: case reports and review of the literature

Alexander Zlotnik · Shaun E. Gruenbaum · Irene Rozet · Agzam Zhumadilov · Yoram Shapira

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Abstract Congenital insensitivity to pain with anhidrosis (CIPA) is a rare autosomal recessive disease, characterized by episodes of unexplained fever, anhidrosis, pain insensitivity despite intact tactile perception, self-mutilating behavior, mental retardation, and autonomic nervous system (ANS) abnormalities. We present a case series of three patients with CIPA who underwent semielective orthopedic surgery under general anesthesia complicated by intraoperative regurgitation, and subsequent aspiration in two of the three cases. All three patients were nil per os (NPO) for at least 8 h prior to surgery. Two patients had their airways maintained with a laryngeal mask airway (LMA), and one patient had an endotracheal tube (ETT). The patients with an LMA suffered aspiration of gastric contents and subsequently developed hypoxic cardiac arrest. Although the patient with an ETT in situ regurgitated intraoperatively, the presence of the ETT prevented aspiration and any further potential complications. We review the perioperative complications typically observed in patients with CIPA and discuss the risks of using an LMA in these patients. We recommend that patients with CIPA always should be considered as having a "full stomach", regardless of the duration of their NPO status, due to their coexisting ANS abnormalities. Therefore, rapid-sequence induction with an ETT should be utilized for the anesthetic management in every patient with CIPA.

Keywords CIPA · Autonomic dysfunction · General anesthesia · Rapid-sequence induction

A. Zlotnik (✉) · Y. Shapira
Department of Anesthesiology and Critical Care,
Soroka Medical Center, Ben-Gurion University of the Negev,
84105 Beer-Sheva, Israel
e-mail: zlotnika@bgu.ac.il

S. E. Gruenbaum
Department of Anesthesiology, Yale University School of Medicine, New Haven, CT, USA

I. Rozet
Department of Anesthesiology and Pain Medicine,
University of Washington, Seattle, WA, USA

A. Zhumadilov
Department of Neuroanesthesiology and Critical Care,
Republican Scientific Center of Neurosurgery,
Astana, Kazakhstan

Introduction

Congenital insensitivity to pain with anhidrosis (CIPA) is a rare, autosomal recessive disease classified as a type IV hereditary sensory and autonomic neuropathy [1, 2]. CIPA is linked to a mutation in the tyrosine kinase gene [1, 2]. Clinical manifestations of CIPA include unexplained fever, anhidrosis, insensitivity to pain with intact tactile perception, self-mutilating behavior, mental retardation, and autonomic nervous system (ANS) abnormalities [3]. The anomalous pain and temperature sensations result from the absence of afferent neuronal activation, while the anhidrosis is due to the loss of exocrine sweat gland innervations [2]. Diminished pain perception results in a decreased ability to protect oneself from external or self-inflicted damage. Therefore, children with CIPA often sustain severe and unrecognized injury. Painless fractures and self-inflicted injuries to the fingers, lips, and tongue are commonly seen in patients with CIPA. Recurrent episodic fevers are usually the first clinical sign of CIPA in infancy or early childhood [2]. Because children with CIPA do not sweat, they often develop hyperthermia when exposed to high environmental temperatures, which can even lead to

death due to hyperpyrexia [1, 2, 4–6]. Insensitivity to pain may result in bone fractures, skin infections, multiple scars, osteomyelitis, and joint deformities. In contrast to patients with familial dysautonomia, emotional tearing is normal, there is no acrocyanosis, and cardiovascular responses are normal in the early years. A previous report [7] described that gastrointestinal dysmotility is infrequent, with vomiting not a feature of the disease.

This rare disease is a challenge for anesthesiologists because of the high risk of anesthetic complications that result from the patients' ANS abnormalities, including hyperthermic events and hemodynamic instability, particularly hypotension and bradycardia [5, 6, 8, 9]. Here we present three cases of intraoperative regurgitation under general anesthesia in patients with CIPA; the patients who where managed with a laryngeal mask airway (LMA) suffered massive aspiration of gastric contents resulting in hypoxia and subsequent cardiac arrest. The patient in whom the airway was maintained with an endotracheal tube (ETT) did not aspirate despite massive regurgitation.

Case descriptions

All three patients were nil per os (NPO) for solids and liquids for at least 8 h. Venous access had been obtained before injecting the anesthetics. Standard monitors were utilized, including electrocardiogram (ECG), noninvasive blood pressure (NIBP), pulse-oximeter, end-tidal carbon dioxide ($ETCO_2$), nasopharyngeal core body temperature, and an oxygen analyzer.

Case 1

A five-year-old boy, 17 kg in body weight and with body temperature of 37°C, with CIPA presented for a semi-elective toe amputation and right leg wound debridement due to osteomyelitis of the toe and an infected wound of the right leg. The patient was known to have undergone general anesthesia at least three times in the past, for which the only complication under anesthesia noted was hemodynamic instability (arterial hypotension). Both an LMA (once) and an ETT (twice) had been used during the previous surgeries.

The patient's airway was assessed as having no anomalies predicting a difficult airway. The Mallampati score was not assessed due to mental retardation.

After preoxygenation, anesthesia was induced with an intravenous injection of propofol of 2 mg/kg, followed by the insertion of an LMA size 2.5, and the patient was breathing spontaneously during the surgery. The anesthesia was maintained with isoflurane (end-tidal 1.5%) and nitrous oxide in oxygen at a ratio of 1:1. In our institution, we have widely used LMAs to manage pediatric airways for peripheral, short procedures in patients older than 1 year, with a low rate of airway-related complications.

Forty minutes after the surgery had started, the patient regurgitated a large amount of gastric contents, and solid particles of food appeared in the mouth and the throat. The laryngeal mask was immediately removed, the regurgitated contents were cleared by a large-bore suction tube from the pharynx, and the patient was ventilated by face mask with 100% oxygen. The trachea was then intubated with a cuffed ETT (internal diameter [ID] 5.0 mm) without the use of any additional medications. The trachea was suctioned through the ETT, and particles of gastric contents were removed from the trachea.

Subsequently, the patient developed extreme hypoxemia (arterial oxygen saturation [SpO_2] $< 50\%$) followed by extreme bradycardia (heart rate [HR] < 20 beats/min). His $ETCO_2$ dropped to zero, reflecting cardiac arrest. The surgery was halted, and cardiopulmonary resuscitation (CPR) was initiated. During resuscitation the patient received 0.2 mg epinephrine and 0.2 mg atropine intravenously. Spontaneous cardiac and peripheral pulse activity resumed after 5 min of CPR. The blood pressure remained low (60/30 mmHg), and norepinephrine infusion was initiated at a rate of 3 μg/min. The surgery was continued and completed within 15 min.

After completion of the surgery, the patient remained mechanically ventilated and was transported to the pediatric intensive care unit (PICU). Gastric content pH was not measured. The patient continued to be hypoxemic for 2 days thereafter (PaO_2 50–60 mmHg, fractional inspired oxygen [FiO_2] 1.0). A chest X-ray revealed bilateral diffuse infiltrates, which completely resolved within a few days. The patient was discharged from the hospital 10 days after the event without any neurological or cardiovascular sequelae.

Case 2

A six year-old girl, 15 kg in body weight and with body temperature of 36.7°C, with CIPA presented for a semi-elective left hip wound debridement, due to osteomyelitis and wound infections of her left femur. Her previous history of general anesthesia (five times) was uncomplicated. Both an LMA and an ETT had been utilized during the previous surgeries.

Almost 2 years had elapsed after the surgery in case 1, and the anesthesiologist was unaware of the complication in case 1. Therefore, the anesthesiologist did not change his approach to the airway management to prevent possible aspiration. After preoxygenation, anesthesia was inducted with propofol at 2 mg/kg. A size 4 LMA was applied, and the patient was breathing spontaneously during the surgery.

Maintenance of anesthesia was achieved using isoflurane (end-tidal 1%) and nitrous oxide in oxygen at a ratio of 1:1. The patient did not receive any opiates because she was insensitive to pain.

The patient suddenly regurgitated a large volume of gastric contents 20 min after the start of surgery. The regurgitated contents included solid particles of food. The LMA was immediately removed, the gastric vomitus was cleared using a large-bore suction tube, and the patient was ventilated with a face mask with 100% oxygen. The trachea was then intubated with a cuffed ETT (ID 5.0 mm), and tracheal suction was performed through the ETT.

The patient developed severe hypoxia (oxygen saturation dropped to <60%) followed by asystole. The surgery was stopped, and CPR was initiated. During the resuscitation, the patient received 0.2 mg epinephrine intravenously and 0.2 mg atropine sulfate intravenously. Spontaneous cardiac and peripheral pulse activity resumed after 3 min of CPR. The blood pressure remained low (about 55/25 mmHg), and an intravenous infusion of norepinephrine was initiated at a rate of 3 μg/min. The surgery was then resumed and finished within 20 min.

After completion of the surgery, the patient was transported to the PICU, where she remained hypoxemic for 2 days. Again, gastric content pH was not measured. A chest X-ray revealed bilateral diffuse infiltrates, which completely resolved within a few days. The patient was discharged from the hospital 8 days after the event without any neurological or cardiovascular sequelae.

Case 3

A seven-year old girl was scheduled for semielective orthopedic surgery for a leg wound debridement due to infected wounds of the right leg. She had previously undergone general anesthesia five times without any complications. On examination, the patient was malnourished (weight of 16 kg), the patient's body temperature was 36.3°C, and she was NPO for 10 h.

The patient's airway was assessed and this did not reveal anything that would predict a difficult airway. The Mallampati score was difficult to assess properly due to very limited patient cooperation secondary to mental retardation. Considering that only 2 weeks had passed since the aspiration described in case 2, the anesthesiologist (the same person that treated the patient described in case 2) considered the patient as having a full stomach and decided to manage the patient's airway with a rapid-sequence induction.

After preoxygenation, anesthesia was induced with an intravenous injection of propofol 2 mg/kg, and atracurium 10 mg was given to facilitate endotracheal intubation. The trachea was intubated without any difficulties with an uncuffed ETT (ID of 5.5 mm) under the Sellick maneuver without mask ventilation. We routinely use uncuffed ETTs in pediatric patients under age eight to prevent possible airway edema in the subglottic area secondary to pressure-induced mucosal injury. The proper size of the ETT was checked with a small air-leak test at about 25 cm H_2O. Positive-pressure ventilation was utilized during the surgery: pressure control mode, peak inspiratory pressure limit of 25 cm H_2O, respiratory rate of 16 per minute. No positive end-expiratory pressure was applied. Maintenance of anesthesia was achieved using 0.5–1.5% isoflurane and nitrous oxide in oxygen at a ratio of 1:1. The isoflurane concentration was adjusted to maintain the blood pressure in the normal range and prevent hypotension. Opiates were not used because the patient was insensitive to pain.

The surgery lasted 1 h. Unfortunately, gastric decompression had not been performed either before the induction of general anesthesia or after intubation. Ten minutes before the surgery was completed the patient vomited, and the gastric contents included particles of food. Suction of both the pharynx and trachea was performed immediately. No traces of gastric contents were observed in the trachea. A nasogastric (NG) tube was inserted into the stomach and 35 ml of gastric fluid was drained. The surgery was resumed, and the patient's respiration and hemodynamics remained stable for the rest of the surgery. Recovery from anesthesia and the surgery was uneventful, and the patient was discharged home on the third postoperative day in good condition.

Discussion

We present here for the first time three patients with CIPA who suffered intraoperative regurgitation; two of these patients aspirated. CIPA is a rare hereditary sensory autonomic neuropathy [1, 2]. To date, only 52 cases have been reported in the literature worldwide [6, 8, 9]. The majority of CIPA cases have been described in Israel and Japan. In Israel, there are two known Bedouin families in the southern region of Israel in which CIPA has been documented. In one family, a 1926-ins-T mutation in the tyrosine kinase domain or the *TrkA* gene has been described. In the other family, a Pro-689-Leu mutation has been found [9]. The anesthetic management of patients with CIPA is challenging because of the increased risk of complications related to ANS abnormalities, such as hyperthermia and cardiovascular instability [5, 6, 8, 9].

Historically, impaired temperature control has been considered a primary anesthetic concern in patients with CIPA. Hyperpyrexia has been shown to cause death in about 20% of affected patients within the first 3 years of life [10]. Strict perioperative temperature control has been

recommended to maintain a core body temperature not higher than 37°C [4–6, 8, 9, 11]. Intraoperative hemodynamic instability with hypotension and bradycardia has also been reported [3, 5, 6, 8–11]. Recent case series and retrospective studies have failed to demonstrate the previously described hyperpyrexic events [5, 6, 8]. Two large series from Japan and Israel failed to demonstrate even a single case of perioperative hyperthermia, despite a lack of prophylactic measures to prevent this potential complication [6, 8]. However, analysis of the literature clearly demonstrates that perioperative vomiting is a common problem in patients with CIPA [4, 8, 12].

Thus far, little attention has been paid to the risk of regurgitation and aspiration in patients with CIPA during the perioperative period [6, 12]. The ANS abnormalities in patients with CIPA may predispose to gastroparesis, delayed gastric emptying, and an increased risk for regurgitation and aspiration, much like in diabetic patients [13]. However, gastrointestinal dysmotility is infrequent in patients with CIPA, and vomiting is not a feature of the disease [7]. Nonetheless, there may be some degree of delayed gastric emptying.

Unfortunately, there are no data available that determine the gastric emptying time, gastroesophageal sphincter tonus, and pH of the gastric contents in CIPA. There are great difficulties in performing such studies given the low prevalence of CIPA and its unhomogeneous distribution. Furthermore, there are no strong recommendations for the airway management of these patients. Neither the use of an LMA nor that of an ETT has been discussed.

All three patients discussed here were NPO for solids and liquids for at least 8 h. A fasting period of 6 h is accepted to be sufficient for gastric emptying in children older than 36 months after nonhuman milk or a light meal. In the case of ingesting heavy meals, gastric emptying may be delayed and it is therefore recommended to prolong preoperative fasting [14]. As such, 8 h should be more than enough time for the passage of food from the stomach in patients with normal gastric motility.

In a case series of six patients [4] with CIPA anesthetized with thiopental and succinylcholine, three patients vomited in the postoperative period. In another retrospective study, two of 15 patients vomited in the PACU after general anesthesia, and one of them had severe vomiting [8]. Interestingly, treatment with common antiemetic drugs had no effect in those patients. The authors concluded that the development of postoperative vomiting in CIPA patients was not caused by the usual mechanisms observed in non-CIPA patients [8].

One case report from Japan described a patient with CIPA who developed long-lasting postoperative vomiting after anesthesia maintained with nitrous oxide and sevoflurane [12]. The use of propofol-based anesthesia and the avoidance of anesthetic gases did not lead to postoperative vomiting in the same patient after a later operation. The aforementioned reports suggest an increased incidence of perioperative vomiting in patients with CIPA. Surprisingly, the potential causes have not been previously discussed in the literature. We propose that the delayed gastric emptying due to ANS dysfunction leads to perioperative regurgitation and aspiration in patients with CIPA, even though vomiting is not typical for these patients [7].

Intraoperative cardiac arrest that resulted in the death of a patient with CIPA has been reported previously [6]. No definitive airway had been maintained in this patient, as the patient was breathing spontaneously with an LMA. Because the patient's parents declined an autopsy, precluding the possibility of determining the exact cause of death, silent regurgitation and aspiration of gastric contents could not be excluded. The authors of that report remarked that they could not rule out hypoxia or hypoventilation as a cause of the cardiac arrest.

Although an LMA is widely utilized today for airway management in both the adult and pediatric populations, the use of an LMA does not reliably protect the lungs from regurgitated gastric contents [15]. If placed improperly, an LMA may in itself predispose to regurgitation if displaced during an operation, causing an air leak and subsequent inflation of the stomach. An assessment of the risk of aspiration is vital in determining whether an LMA can be safely used [15]. Patients with CIPA do not usually require analgesics for the maintenance of anesthesia, and are prone to become hemodynamically unstable with high concentrations of either volatile or intravenous anesthetics. Thus, using superficial anesthesia might predispose to eliciting the gag reflex from stimulation of the pharynx with an LMA, and may therefore induce vomiting.

The development of laryngospasm is another threatening complication of an LMA, especially when anesthesia is superficial or multiple attempts to insert the LMA are needed [16]. Attempts to resolve this condition with positive-pressure ventilation typically lead to gastric inflation and increase the risk of regurgitation. Because an LMA does not prevent the aspiration of gastric contents into the trachea, the use of an LMA for airway management does not seem appropriate for patients with CIPA. Interestingly, an LMA has been used successfully, though infrequently, for airway management in patients with CIPA without any complications [8]. However, in a case of a cardiac arrest described in a 19-month-old patient with CIPA, this occurred while an LMA was used for airway management [6].

We presented three cases demonstrating an increased risk of the aspiration of gastric contents during general anesthesia in patients with CIPA, followed by hypoxia and cardiac arrest in two out of three cases. One case illustrates that aspiration can be prevented by endotracheal intubation

with an ETT. It is important to note that each patient had undergone multiple surgeries under general anesthesia in the past, with both ETTs and LMAs used for airway management. No cases of vomiting or aspiration had been observed irrespective of the airway management. There are several possible explanations for this. There may have been differences in the amount of food eaten before the procedures, in preoperative stress (which may affect gastric emptying), in the motility and tonus of the lower esophageal sphincter with time, in the length of the procedures, or in the anesthetic techniques used. Furthermore, even in subjects with full stomachs, aspiration is not always observed.

Based on our experience, we recommend that all patients with CIPA should be managed as patients with a "full stomach", regardless of NPO status, requiring rapid-sequence induction with the Sellick maneuver and an endotracheal intubation to prevent life-threatening anesthetic complications. The use of metaclopramide, sodium citrate, and H2 histamine-receptor antagonists may be justified in these patients before the induction of anesthesia to prevent the regurgitation of gastric contents, and the suctioning of gastric contents using a naso- or orogastric tube during the surgery can be also considered. Studies to elucidate gastric emptying time, esophageal sphincter tonus, and gastric pH in patients with CIPA are needed.

Conclusions

The perioperative management of patients with CIPA remains a challenge for anesthesiologists because of the high risk of anesthetic complications resulting from ANS irregularities. As such, patients with CIPA are at increased risk for regurgitation of gastric contents, aspiration, and life-threatening hypoxia. We recommend that all patients with CIPA should be managed as patients with a "full stomach". Therefore, rapid-sequence induction with cricoid pressure (Sellick maneuver), intubation of the trachea with an ETT, and nasogastric suctioning of gastric contents should be utilized to prevent life-threatening anesthetic complications.

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