Perioperative care of a child with Crisponi syndrome

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Crisponi syndrome is an autosomal recessive disorder characterized by intermittent episodes of muscular contraction of the facial muscles with trismus and excessive salivation simulating a tetanic spasm. These episodes occur in response to tactile stimulation or during crying. Associated physical and constitutional findings include characteristic facial anomalies, camptodactyly, intermittent hyperthermia, and feeding difficulties. We present a 15-month-old girl who required anesthetic care during laparoscopic fundoplication and gastric tube insertion. The perioperative implications of the disorder are reviewed and suggestions for anesthetic management provided.

Introduction

Crisponi syndrome was first described in a cohort of 17 patients from a total of 12 families. It is an autosomal recessive disorder that is characterized by the neonatal onset of episodes of marked muscular contraction of the facial muscles with trismus and excessive salivation simulating a tetanic spasm. These episodes occur in response to tactile stimulation or during crying. Additional features include characteristic facial anomalies, intermittent hyperthermia, and feeding difficulties. It is usually lethal during the first year of life. We present a 15-month-old girl who required anesthetic care laparoscopic fundoplication and gastric tube insertion. The perioperative implications of the disorder are reviewed and suggestions for anesthetic management provided.

Case report

Institutional Review Board approval is not required at King Fahad Medical City (Riyadh, Saudi Arabia) for publication of isolated case reports. A 15-month-old, 9.2 kilogram girl presented for laparoscopic fundoplication and gastrostomy tube insertion. Associated problems included generalized hypotonia, swallowing difficulties, GERD, recurrent respiratory infections, dysmorphic facial features as noted in Fig. 1 (rounded face, poorly developed and depressed nasal bridge, anteverted nares, long philtrum, high-arched palate and micrognathia), low-set ears, cubitus valgus with flexion deformities at the elbows, intermittent contracture of the facial muscles, puckering of the lips, and drooling of foamy saliva when crying. Past medical history included dilated

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cardiomyopathy secondary to sepsis with a respiratory infection 5 months ago. The patient’s cardiac function had improved since then and she was on no cardiac medications and recent echocardiogram showed normal function. One month ago, hydrocephalus was noted on computed tomography imaging and a ventriculoperitoneal shunt was inserted. She also had mild thoracolumbar scoliosis with an angle of 20° (Fig. 2). The child was the product of a full term gestation, delivered by Cesarean section due to breech presentation with history of a consanguineous marriage. The only other sibling died had died suddenly during infancy, having been diagnosed with Crisponi syndrome. Medications included domperidone 2 mg per nasogastric (NG) tube every 6 hours, omeprazole 10 mg per NG once a day, flixotide 50 µg via metered-dose inhaler (MDI) every 12 hours, and albuterol via MDI every 6 hours. Vital signs included a heart rate of 120 beats/minute, blood pressure of 100/52 mmHg, a room air oxygen saturation of 96%, respiratory rate of 28 breaths/minute, and a temperature of 37°C. The patient had a 24 gauge intravenous cannula in place. She was transported to the operating room and standard American Society of Anesthesiologists’ monitors were placed. Anesthesia was induced with the inhalation of sevoflurane in 100% oxygen. After effective bag-valve-mask ventilation was demonstrated, propofol (2 mg/kg) and ketamine (2 mg/kg). Endotracheal intubation was performed on the first attempt with a 4.0 cuffed ETT using indirect laryngoscopy (Glidescope®). Neuromuscular blockade was then provided using a single dose of rocuronium (0.5 mg/kg). A second peripheral intravenous cannula and a radial artery cannula were inserted. Anesthesia was maintained with sevoflurane (expired concentration of 2-3%) and fentanyl 4 µg/kg. Surgical duration was approximately 2 hours. Estimated blood loss was minimal. Intraoperative fluids included 130 mL of lactated Ringer’s solution. At the completion of the procedure, residual neuromuscular blockade was reversed with neostigmine and the patient’s trachea was extubated. Postoperative analgesia was provided by morphine and paracetamol (15 mg/kg) with infiltration of bupivacaine 0.25% at the port sites. She was admitted to the Pediatric ICU for postoperative observation of her respiratory status. She was discharged to the inpatient ward after 24 hours and was discharged home on postoperative day 7. Her postoperative course was unremarkable.

**Fig. 1**
Photograph of our patient demonstrating typical facial features of Crisponi syndrome including chubby cheeks, broad nose, depressed nasal bridge with anteverted nares, and micrognathia

**Fig. 2**
Radiographs of the face and spine showing mid-face hypoplasia and scoliosis

**Discussion**

Crisponi syndrome is a rare autosomal recessive syndrome, described in 1996 by Crisponi, which is caused by mutations in the CRLF1 gene. It has been reported in fewer than 30 patients from 13 Italian families, most from Sardinia and is generally lethal during the first year of life. Although postulated to be a distinct syndrome, similarities exist between the Crisponi phenotype and Freeman-Sheldon syndrome, the severe form of Schwartz-Jampel type 2, and Stuwe-Wiedemann syndrome (SWS). The phenotype is characterized by muscular contractions at birth, facial abnormalities (chubby cheeks, broad nose with anteverted nares, and long philtrum as noted in Fig. 1), camptodactyly (Fig. 3), and episodes of unexplained hyperthermia. Early in the neonatal period, patients with Crisponi syndrome develop continuous hyperthermia unrelated to infectious or other etiologies,
Crisponi syndrome can be confirmed by testing for mutations in the genes cardiotrophin-like cytokine factor 1 (CLCF1) or cytokine receptor-like factor 1 (CRLF1). These two proteins function together to form a unit known as the CRLF1/CLCF1 protein complex. This complex attaches to a receptor protein known as the ciliary neurotrophic factor receptor (CNTFR) on the surface of many types of cells. When the CRLF1/CLCF1 protein complex is bound to CNTFR, it triggers signaling within the cell that affects cell development and function. Defects of the proteins coded by CLCF1 and CRLF1 disables the CNTFR signaling pathway. At least four different mutations in the CLCF1 gene have been reported to cause cold-induced sweating syndrome resulting in hyperthermia and disorders of body temperature regulation. The CNTFR pathway’s involvement in motor neuron and bone development provides clues to the other signs and symptoms of Crisponi syndrome including distinctive facial features, facial muscle weakness, and skeletal abnormalities.

As with all anesthetic care, appropriate preoperative preparation begins with a thorough history and physical examination. Patients with known genetic syndromes pose a variety of challenges to the anesthesia provider including the potential for difficulties with airway management. To date, there are no previous reports regarding the anesthetic care of patients with Crisponi syndrome; however, given the phenotypic facial features as noted in our patient (micrognathia and a high-arched palate), potential difficulties with bag-valve-mask ventilation or endotracheal intubation should be anticipated. The appropriate equipment for dealing with the difficult airway should be readily available prior to anesthetic induction. As was performed in our patient, general anesthesia can be induced by the incremental inhalation of sevoflurane in 100% oxygen with the maintenance of spontaneous ventilation until effective bag-valve-mask ventilation is demonstrated. Once effective bag-valve-mask ventilation was demonstrated, the depth of anesthesia was deepened with the administration of ketamine and propofol followed by indirect laryngoscopy and endotracheal intubation using the Glidescope®. Airway management may be further compromised by the risk of aspiration due to gastroesophageal reflux which may suggest the need for rapid sequence intubation (RSI). However, the use of RSI must be weighed against the risks of potential difficulties with airway management and endotracheal intubation.

Regardless of the etiology, hypotonia may affect perioperative care, impacting decisions regarding the use of neuromuscular blocking agents (NMBAs), especially with regards to the safety of using succinylcholine. Given the lack of previous reports regarding anesthetic care of patients with Crisponi syndrome, there are no data on which to base recommendations regarding the use of succinylcholine. Given the anticipated duration of the procedure and clinical circumstances, rocuronium was chosen for our patient. Given the intraoperative requirements for the surgical procedure, a low dose of rocuronium (0.5 mg/kg) was effective without the need for repeated dosing. No prolongation of effect was noted and neuromuscular blockade was reversed completely at the completion of the procedure with neostigmine. However, non-depolarizing NMBAs should be used with care as the effect can be prolonged even with routine dosing in patients with pre-existing neuromuscular diseases or hypotonia. Alternatively, where available, sugammadex may provide an additional margin of safety for reversal of the neuromuscular blocking effects of rocuronium or vecuronium.
The majority of patients with Crisponi die in the neonatal period or in early childhood. Recurrent episodes of unexplained hyperthermia unrelated to exposure to anesthetic agents are the cause of death in most cases. Cold-induced sweating develops usually at a later age. The pathogenesis of hyperthermia is complex. Once the body temperature reaches a critical level (>41.5°C), heat stress activates an acute-phase response with systemic inflammation and coagulation disturbances. This results in multi-organ system failure including encephalopathy, rhabdomyolysis, acute renal failure, and disseminated intravascular coagulation. Many different disease processes, environmental situations, and systemic stresses can initiate this response. Avoidance of stimuli known to cause hyperthermia and active maintenance of euthermia are important considerations in preventing critical hyperthermia and its fatal consequences.

Abnormal central control of respiration with apnea has been reported in patients with Crisponi syndrome. This finding, autonomic dysfunction with hyperthermia, paroxysmal muscular contractions, and trismus suggests supports the hypothesis of brainstem dysfunction as the etiology of sudden death in Crisponi Syndrome.

One additional perioperative concern is the potential for postoperative respiratory dysfunction and failure. Chronic or acute aspiration may result in respiratory dysfunction which may be potentiated by associated hypotonia and abnormal central control of ventilation. As such, close monitoring of postoperative respiratory function is suggested, preferably in an ICU setting. While effective pain control is essential, associated respiratory and central nervous system involvement may predispose these patients to respiratory depression with opioids. As such, adjunctive agents including non-opioid analgesics (paracetamol) and local/regional anesthesia are suggested to limit perioperative opioid requirements.

Crisponi syndrome is a rare autosomal recessive disorder that was first reported in the literature in 1996. Given the associated feeding difficulties, anesthetic care may be required for fundoplication or placement of a gastroscopy tube. Potential perioperative concerns include phenotypic features which may make airway management challenging, spontaneous episodes of profound hyperthermia, brainstem dysfunction with defective central control of ventilation, hypotonia, and chronic lung disease related to aspiration.
References


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† Train-of-four
‡ Post-tetanic counts
§ Second twitch


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