The following case report describes a 13-year-old child with alternating hemiplegia of childhood (AHC) who underwent magnetic resonance imaging MRI with general anesthesia and experienced a hemiplegic spell, seizure, apnea, and sudden cardiac arrest with successful resuscitation. AHC is a rare neurodevelopmental disorder characterized by repeated episodes of weakness or paralysis affecting one or both sides of the body and multiple other neurologic problems. The challenges associated with this disorder include management of developmental delay, dystonia, hemiplegia, cerebrovascular dysfunction, apnea, and autonomic dysfunction. The current literature is extremely limited in describing the effects of general anesthesia for a patient with AHC. While the neurologic manifestations of AHC are well described, autonomic dysfunction and the potential for sudden cardiac arrest have not been widely reported. To our knowledge, this is the first case report to emphasize anesthetic considerations in a pediatric patient with AHC, specifically the unrecognized potential for cardiac arrhythmia and sudden cardiac arrest.

Keywords: Alternating hemiplegia of childhood, anesthesia, ATP1A3, pediatrics, short QTc

Anesthetic Implications in Alternating Hemiplegia of Childhood: A Case Report

Emily M. Funk, DNP, CRNA
Mohamad A. Mikati, MD
Andrew P. Landstrom, MD, PhD
Mary E. Moya-Mendez, MS
Keri R. Wallace, BS
Milton O. Pratt, BS
Matthew E. Heyes, DNP, CRNA
Guy Dear MA, MB, BChir, FRCA, FUHM

Alternating hemiplegia of childhood (AHC) is a neurodevelopmental disorder characterized by infantile onset of episodes of hemiplegia, dystonia, seizures, cognitive disturbances, and oculomotor impairment. The prevalence of AHC is 1:1,000,000. Approximately 75% of patients with AHC have a genetic variant of the ATP1A3 gene. Symptoms of a characteristic AHC episode include nystagmus, vaso-motor prodrome with abrupt onset of hemiplegia, and dystonia (possibly with seizures and dyskinetic movements). Patients with AHC often experience central and obstructive sleep apnea (OSA), autonomic dysfunction, and increased risk for mortality. The potential for cardiac arrhythmias is not well reported but is a particular risk for the 75% of patients with AHC who express the ATP1A3 gene variant that encodes the alpha subunit of the Na⁺/K⁺-ATPase pump and is expressed not only in neurologic but also in cardiac tissues.

The patient undergoes tests to rule out associated comorbidities and inform diagnosis and management when AHC is suspected. Patients with AHC may require general anesthesia to undergo these diagnostic tests, which may include electroencephalograms, sleep studies, electrocardiograms (ECG), muscle biopsies, and magnetic resonance imaging (MRI).

CASE SUMMARY

A 43-kg, 13-year-old pediatric patient with AHC presented for an MRI with general anesthesia to assess severe headaches and increased frequency of AHC episodes occurring two times per week. His first described episode of hemiplegia occurred with nystagmus on the first day of life followed by an episode of double hemiplegia first noted at age 8 months. He continued to have symptoms of nystagmus, dystonia, predominance of spells on the right side of his body, and developmental regression which were occasionally noted throughout the following years, until age 6 years when he first began to have seizures. He was initially diagnosed with epilepsy and then subsequently was diagnosed with AHC via genetic testing that
showed an ATP1A3-D801N variation. His AHC episodes, reported to include dystonia and loss of vision, were managed using flunarizine and melatonin with resolution of his spells during sleep. His AHC history also included a report of mitochondrial dysfunction and a skeletal muscle oxidative defect noted from a muscle biopsy.

On the day of service, his caregiver reported to the anesthesia team that his history also included resolved OSA, irritability, self-injurious behavior, and episodes of psychosis. His baseline neurologic status on the day of the MRI indicated an alert individual with intact vision and hearing who asked questions but was slow to provide verbal responses. The patient had no history of syncope or unexplained loss of consciousness. He was under the care of a cardiologist because of his AHC; an ECG performed at age 7 years showed normal sinus rhythm with sinus arrhythmia and normal intervals, including a corrected QT interval (QTc) of 364 ms. Echocardiogram at the same age demonstrated normal intracardiac anatomy. The cardiology team recommended checks of his heart function every 1-2 years, or more frequently if any concerns arose. He received 24-hour cardiac Holter monitoring approximately every 2 years, which continued to demonstrate a normal baseline with mild sinus bradycardia and mild sinus tachycardia. His prior general anesthetics were reported as uneventful and included an MRI at age 8 months, a muscle biopsy, a tonsillectomy, and adenoidectomy at unknown ages. His home medications included guanfacine, risperidone, clonazepam, flunarizine, trazodone, diazepam, and divalproex sodium.

This patient was referred for MRI under general anesthesia because he had MRI performed with nonanesthesia sedation team at age 11 years during which he experienced bradycardia with dexmedetomidine sedation (initial bolus of intravenous [IV] 1.5 mcg/kg given over 5 minutes but was stopped at 3 minutes due to bradycardia of 45 beats per minute [bpm] with reported junctional beats). He was given a 20-mL/kg normal saline bolus, and MRI was completed with a dexmedetomidine infusion at 1 mcg/kg/hour. On the day of the current case report, the patient did not tolerate a peripheral IV catheter in holding due to aggressive and developmentally delayed behavior. Therefore, anesthesia was induced by inhaled sevoflurane, and an IV catheter was placed after induction. A supraglottic airway (SGA) was placed without difficulty. Sevoflurane was continued for maintenance of anesthesia and the patient breathed spontaneously with pressure support and a backup mode of automatic initiation of synchronous positive pressure ventilation in the event of apnea. MRI was completed without incident. Vital signs including heart rate, blood pressure, respiratory rate, and end tidal carbon dioxide remained stable throughout. The SGA was removed while the patient was at a deep level of anesthesia, as is routine at our institution.

Vital signs prior to the SGA removal included heart rate of 60 bpm, blood pressure of 95/48 mmHg, respiratory rate of 18, and end tidal carbon dioxide of 35 mmHg. Shortly after the SGA was removed and the inhalation agent was discontinued, the patient developed bradycardia of 50 bpm with a blood pressure of 90/46 mmHg despite spontaneous ventilation and oxygen saturation (SpO₂) of 100%, and 0.2 mg IV glycopyrrolate was administered. Bradycardia of 30 bpm rapidly followed with a blood pressure of 87/42, and 0.2 mg IV atropine was given. The patient’s response to the atropine was an increase in heart rate to 120 bpm and in blood pressure to 135/91. Oxygen was provided at 8 L/minute with a partial rebreather face mask, and he maintained spontaneous ventilation with SpO₂ at 97%.

Upon full emergence, the patient became agitated and combative, purposefully pulling off all monitors. He was treated with 16 mcg (0.37 mcg/kg) IV dexmedetomidine titrated over approximately 10 minutes with a satisfactory calming result. SpO₂ monitoring was reestablished, and oxygen saturation of 100% was achieved with administration of 8 L/minute of oxygen via partial rebreather face mask. He continued to maintain spontaneous ventilation.

The patient was monitored by transport pulse oximetry while being transferred to the recovery room, but within 1-2 minutes after leaving the MRI suite, he exhibited irregular breathing and “seizure-like movements.” Midazolam 0.05 mg/kg IV was administered as treatment for this activity, but the patient became simultaneously pale and cyanotic; this was followed by apnea, unresponsiveness, and a subsequent decrease in SpO₂ such that providers could not obtain a reading. The anesthesia team called for a crash cart and additional assistance. Bag-valve mask ventilation was provided with adequate chest rise. No palpable pulse could be detected, chest compressions were commenced, and epinephrine 10 mcg/kg IV was administered. Endotracheal intubation was performed and placement was confirmed. The defibrillator and ECG were attached to the patient, and ventricular fibrillation was identified on the ECG. The patient was then defibrillated at 2 J/kg. After a second round of cardiopulmonary resuscitation with administration of lidocaine, epinephrine, and sodium bicarbonate followed by a second defibrillation at 2 J/kg, the patient had a return of spontaneous circulation with a rapid narrow complex tachycardia >180 bpm. The rhythm was terminated by synchronized cardioversion at 0.5 J/kg. Heart rate returned to a stable sinus rhythm of 76 bpm with a blood pressure of 143/87 mmHg. An arterial line was placed, and the patient was transferred to the pediatric intensive care unit (PICU).

The patient remained intubated in the PICU, sedated, and on an epinephrine infusion with systolic blood pressure maintained at 90-120 mmHg. Because epinephrine
was the vasopressor that had successfully terminated the ventricular fibrillation, it was continued in the immediate postresuscitation period. An echocardiogram performed approximately 1 hour post cardiac arrest was significant for low-normal right ventricular systolic function and mildly decreased left ventricular systolic function. The cardiology department was consulted and recommended repeat ECGs as well as 24-hour Holter monitoring. The patient displayed no appreciable re-polarization abnormalities during recovery at 24 hours postarrest. He displayed mildly depressed left ventricular systolic function on echocardiography as well as a QTc interval of 416 ms.

His baseline aggressive behavior and episodes of psychosis necessitated administration of lorazepam and haloperidol for agitation prior to extubation in the PICU. On day 3, the patient was extubated to bilevel positive airway pressure for recruitment of atelectatic lung identified by chest radiograph. The chest radiograph demonstrated multifocal opacities and prompted concerns about possible pneumonia and associated suspected aspiration during the cardiac arrest event. On day 6, he was transitioned to high-flow nasal cannula and completed a course of antibiotics for pneumonia previously identified on the chest radiograph. On the seventh day following arrest, his QTc prolonged to a maximum of 470 ms; on the ninth day following arrest, his QTc shortened to 440 ms, and his cardiac function recovered completely. An intracardiac defibrillator placement was discussed but was declined by the family because the patient had demonstrated complete cardiovascular recovery via repeat echocardiography and had no prior history of arrhythmias. Additionally, the family expressed concerns for his quality of life, felt that he would not tolerate placement, and feared that his behavior disorder placed him at increased risk for damage to the device. The patient was discharged from the hospital on day 10 with complete return to his baseline neurologic status.

**DISCUSSION**

Management of patients with AHC has focused largely on the neurologic expressions of the disease. Patients with AHC are at risk for seizures, hemiplegia spells, and apnea, all of which may potentially occur before, during, or immediately following general anesthesia. The current literature on anesthesia offers little guidance to the best approach when providing anesthesia to patients with AHC. Equally insufficient are reports of the interactions between autonomic dysfunction, apneic episodes, and potential for sudden cardiac arrest associated with hemiplegic spells when receiving anesthesia.

To our knowledge, there are no published research-based studies to date of pediatric patients with AHC undergoing anesthesia (Table 1). One case report exists in the dental literature of a 4-year-old boy with AHC undergoing dental restoration under general anesthesia with diazepam, nitrous oxide, and sevoflurane; the patient experienced no complications in the perioperative period. The literature on adult patients is similarly insufficient. A “letter to the editor” reports that an obstetric patient with AHC experienced extreme but transient limb weakness and difficulty swallowing after receiving inhalational anesthesia; however, the patient received propofol, midazolam, and fentanyl for a subsequent procedure without incident. The same patient had been described 3 years earlier in what was at that time the only case report about a patient with AHC and anesthesia; she had received general anesthesia with propofol, alfentanil, and rocuronium for a cesarean section and reported no episodes of hemiplegia or weakness 3 months after discharge. The current case report illuminates the need for considerable attention to be paid to the potential for seizure activity, apnea, cardiac arrhythmias, and risk for sudden cardiac arrest in pediatric patients with AHC undergoing procedures requiring anesthesia.

Sevoflurane and isoflurane are widely used inhalational anesthetics. Because of its lack of airway irritant properties, sevoflurane is commonly used in pediatric anesthesia for inhalation inductions; however, sevoflurane alone may have stronger epileptogenic properties than isoflurane. Notably, sevoflurane may sensitize individuals to their own pattern of epilepsy without necessarily evoking sevoflurane-specific epileptic features. At the time that the patient in this case study presented for anesthesia, sevoflurane had been administered 28 times to 10 patients with AHC at our institution with no adverse events. Conversely, in consideration of the epileptogenic potential of sevoflurane, particularly during induction with high concentrations, a total IV anesthetic (TIVA) with propofol could be considered for patients with AHC because propofol is known to increase the seizure threshold. As a possible alternative, if TIVA is not

<table>
<thead>
<tr>
<th>Publication Year</th>
<th>Age in Years at the Time of Anesthetic</th>
<th>Procedure</th>
<th>Anesthetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>4</td>
<td>Dental restoration</td>
<td>Diazepam, nitrous oxide, sevoflurane</td>
</tr>
<tr>
<td>2005</td>
<td>37*</td>
<td>Dilation and curettage</td>
<td>Propofol, midazolam, fentanyl</td>
</tr>
<tr>
<td>2002</td>
<td>33*</td>
<td>Cesarean section</td>
<td>Propofol, alfentanil, rocuronium</td>
</tr>
</tbody>
</table>

* *Same patient receiving two separate anesthetics.*

**Table 1. Literature Search Results for Patients With Alternating Hemiplegia of Childhood Undergoing Anesthesia.**
appropriate, another inhalation agent such as isoflurane can be considered following a sevoflurane induction.

When a diagnosis of AHC is first suspected, patients will undergo various testing to rule out other potential causes for the presenting symptoms, including specific mitochondrial disorders. A hypothesis that AHC etiology is a result of cellular dysfunction has been explored in previous studies and found to be inconclusive. It is notable that this patient had reported AHC-associated mitochondrial abnormalities diagnosed by muscle biopsy and genetic testing. Although the mitochondrial abnormalities associated with AHC have not been well characterized and their significance remains to be determined, mitochondrial disorders are generally considered a contraindication to administration of propofol. Because a single dose of propofol may be appropriate in a patient with a mitochondrial disorder, TIVA with propofol is not recommended due to the lipid carrier composition of long-chain fatty acids and a potential adverse effect on the mitochondrial respiratory chain.

Perioperative prevention and management of seizures in patients with AHC is of significant concern and a challenge to the anesthesia team. The seizures of the patient under discussion were managed on background therapy with divalproex sodium and clonazepam. As benzodiazepines are known to be beneficial for the management of acute seizures, the patient received IV midazolam for treatment of the seizure following emergence from anesthesia. Additional treatment for an acute seizure could have included IV propofol; however, it was avoided given his mitochondrial disorder.

Patients with AHC are predisposed to both obstructive and central sleep apnea. In this case, the patient had previously undergone tonsillectomy and adenoidectomy for presumed OSA. At the time of the current procedure, his OSA was considered resolved and there was no difficulty with ventilation during inhalation induction or SGA placement. Because central sleep apnea was of concern, the patient was allowed to breathe spontaneously during the anesthetic with automatic initiation of positive pressure ventilation in the event of apnea. The presence of sleep apnea increases the risk for cardiac arrhythmias in the general population. There is an increased risk for cardiac arrhythmias, postoperative apnea, and anesthesia complications in patients with AHC, the majority of whom have sleep apnea. A preanesthetic diagnosis of sleep apnea should alert the anesthesia team to careful consideration to 1) the patient’s ability to maintain a patent airway, 2) the method of airway management (mask, SGA, or endotracheal intubation), and 3) the possibility of apneic episodes as well as means of providing ventilation during periods of apnea while under anesthesia.

In addition to the management of apnea and seizures, considerable attention should be paid to the prevention of hemiplegic spells in the patient with AHC. While it is not possible to prevent all hemiplegic incidents, one should be aware of triggers in the perianesthetic environment and potential mitigation maneuvers (Table 2). Provoking factors include excitement, emotional stress, fatigue, trauma, extremes of temperature, illness, loud noises, bright light, and menstruation. Control of these factors includes ensuring a quiet preanesthetic environment, inducing anesthesia in the least distressing manner for a particular patient, maintaining normothermia, and avoiding bright lights and loud noises.

Inhalation anesthetic agents are known to decrease cardiac muscle contractility. In general, sevoflurane does not significantly sensitize the myocardium to the arrhythmogenic effects of catecholamines; of the various agents, it has the least effect on the cardiac conduction system. Of the 289 cases submitted to the 2000 Pediatric Perioperative Cardiac Arrest (POCA) Registry, two were related to sevoflurane and were reportedly a result of cardiovascular depression during induction of

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Table 2. Hemiplegic Attack Provoking Factors and Controllable Factors in the Perianesthetic Environment

<table>
<thead>
<tr>
<th>Provoking Factors for Hemiplegic Attacks</th>
<th>Controllable Factors in Perianesthetic Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bright lights (sunlight, fluorescent bulbs)</td>
<td>Dim lights</td>
</tr>
<tr>
<td>Emotional stress</td>
<td>Least distressing induction possible</td>
</tr>
<tr>
<td>Excitement</td>
<td>Quiet environment</td>
</tr>
<tr>
<td>Extremes of temperature</td>
<td>Maintain normothermia</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Minimize when possible</td>
</tr>
<tr>
<td>Illness</td>
<td>Unavoidable</td>
</tr>
<tr>
<td>Loud noises</td>
<td>Avoid loud noises</td>
</tr>
<tr>
<td>Menstruation</td>
<td>Unavoidable</td>
</tr>
<tr>
<td>Specific foods (chocolate, food dyes)</td>
<td>Maintain nil per os guidelines prior to anesthesia, avoid intravenous dyes if possible</td>
</tr>
<tr>
<td>Trauma</td>
<td>Minimize when possible</td>
</tr>
<tr>
<td>Water (swimming or bathing)</td>
<td>Minimize surgical preparation disinfectant liquid volume</td>
</tr>
</tbody>
</table>
anesthesia. In the updated 2007 POCA Registry, six of 389 reported cases of cardiac arrest were attributed to sevoflurane-related myocardial depression.

Many factors could have contributed to this patient’s increased risk for cardiac arrhythmias, including cardiac conduction abnormalities resulting from his ATP1A3 mutation, the underlying central nervous system pathophysiology of AHC, and his epilepsy. The patient appears to have had an AHC-related episode of agitation and possible epileptic seizure activity that likely triggered a cardiorespiratory event. The underlying pathophysiology of AHC involves spreading depolarization, which has been shown to trigger apnea and arrhythmias in mouse models with epilepsy and AHC. Patients with epilepsy are predisposed to sudden unexpected death in epilepsy (SUDEP) during seizures, including death resulting from cardiac arrhythmias. SUDEP risk factors include male sex, young age at onset of epilepsy, duration of epilepsy longer than 30 years, frequency of seizures of more than one per year, nocturnal seizures, polytherapy of greater than three medications, developmental delay, and poor compliance.

This patient had most of the listed SUDEP risk factors, including male sex, young age at onset of epilepsy, increased frequency of seizures, polytherapy, and developmental delay.

Upon emerging from anesthesia, he exhibited bradycardia and glycopyrrolate was administered. Glycopyrrolate was chosen because the patient’s blood pressure was stable at the time despite the bradycardia. This medication was also selected because of its inability to cross the blood brain barrier and produce an anticholinergic effect in a patient with a history of irritability and aggression. Nevertheless, the patient’s heart rate continued to decrease, and his blood pressure began to decline. The patient was at this point considered to have unstable bradycardia and was administered atropine, as recommended by the Pediatric Advanced Life Support guidelines, after which his heart rate and blood pressure increased; however, moments later, he also became purposefully aggressive, which placed him at risk for physical harm. Central cholinergic syndrome has not been reported as an increased risk for a patient with AHC; however, this patient had a known baseline aggressive behavior disorder, and emergence delirium was anticipated.

Central alpha-2 agonist dexmedetomidine is increasingly the medication of choice for aggression and delirium following emergence from anesthesia because of its ability to provide sedation and anxiolysis along with preservation of respiratory function; however, its hemodynamic effects include transient hypertension through the peripheral alpha-2 receptor activation in vascular smooth muscle, causing vasoconstriction that can be accompanied by bradycardia produced by the baroreceptor reflex when the medication is administered too rapidly. This bradycardic reflex was demonstrated during prior patient MRI with a dexmedetomidine sedation bolus of 1.5 mcg/kg over 5 minutes. In contrast, in the current case, he received 0.37 mcg/kg IV dexmedetomidine over 10 minutes for agitation following emergence from anesthesia. The patient’s heart rate was 120 bpm at the time of dexmedetomidine administration, the medication was titrated over 10 minutes, and he did not experience reflex bradycardia during slower titration. Caution should be taken when administering medications to patients with AHC that can cause bradycardia, and dexmedetomidine boluses should be injected over 10 minutes.

Pathogenic ATP1A3 variants are responsible for AHC in only 75% of patients with the disease, and there are over 34 differing variants within the single gene, the other 25% of patients with AHC present with a different variant etiology. Genotype phenotype correlations have been well established for the neurologic manifestations of AHC. Future research should concentrate on possible genotype phenotype correlations regarding susceptibility to anesthetic complications. Additional knowledge of individual genetic variants and their responses to anesthetics can help guide appropriate medication choices.

This case study identifies a gap in the limited existing literature on anesthetic management for pediatric patients with AHC. In addition to hemispheric spells, dystonia, seizures, OSA, and autonomic dysfunction, some patients with AHC and a variant of the ATP1A3 gene may be at greater risk for cardiac arrhythmias and sudden cardiac arrest. Currently, the best choice of anesthetic agents for a patient with AHC remains unknown. Further research is needed to understand the effects of general anesthesia on patients with specific genetic variants of AHC.

REFERENCES
AUTHORS
Emily M. Funk, DNP, CRNA is an assistant professor of the Duke School of Nursing Nurse Anesthesia Program and a clinical staff CRNA at Duke University Medical Center, Durham, North Carolina. Email: Emily.funk@duke.edu
Mohamad A. Mikati, MD is in the Department of Pediatrics and Neurobiology, Duke University Medical Center, Durham, North Carolina.
Andrew P. Landstrom, MD, PhD is in the Department of Pediatrics, Division of Cardiology and Department of Cell Biology, Duke University School of Medicine, Durham, North Carolina.
Mary E. Moya-Mendez, MS is in the Department of Pediatrics, Division of Pediatric Cardiology, Duke University School of Medicine, Durham, North Carolina.
Keri R. Wallace, BS is in the Department of Pediatrics and Neurobiology, Duke University Medical Center, Durham, North Carolina.
Milton O. Pratt, BS is in the Department of Pediatrics and Neurobiology, Duke University Medical Center, Durham, North Carolina.
Matthew E. Heyes, DNP, CRNA is at Duke University Medical Center, Durham, North Carolina.

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Name: Emily M. Funk, DNP, CRNA
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