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Case Report

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Anesthetic Care of a Child Harboring the *KCNH2* Gene

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Abstract

Epilepsy is a heterogeneous group of disorders characterized by recurrent and generally unprovoked seizures. Genetic mutations may play an important role in the etiology of epilepsy. Over the past few years, genetic mutations in various genes have been identified in patients with epilepsy. One of the more common mutations responsible for seizures involves the *KCNH2* gene. The *KCNH2* gene encodes the Kv11.1 protein, which involves the pore-forming subunit of a rapidly activating-delayed rectifier potassium channel. This channel plays an essential role in phases 2 and 3 of the cardiac action potential involving cardiac repolarization as well as being expressed in various parts of the central nervous system where it regulates neuronal function. As such, patients presenting with this gene mutation may be at risk not only for seizures, but also abnormalities in cardiac repolarization leading to lethal arrhythmias. We present an 11-year-old girl who required general anesthesia for magnetic resonance imaging as part of her evaluation for non-convulsive status epilepticus. An epilepsy gene panel evaluated revealed a *KCNH2* gene mutation. End-organ involvement of *KCNH2* gene mutations is presented, previous reports of anesthetic care for these patients are reviewed, and options for anesthetic care are discussed.

Keywords: Seizures; Arrhythmia; QT interval; Long QT syndrome; *KCNH2* gene

Introduction

Epilepsy is a heterogeneous group of disorders characterized by recurrent and generally unprovoked seizures. Genetic factors may play an important etiologic role in epilepsy, especially in patients with refractory epilepsy. Over the past years, there has been increased interest in and ability to identify genetic mutations in various genes causing epilepsy. The *KCNH2* gene encodes the Kv11.1 protein, which involves the pore-forming subunit of a rapidly activating-delayed rectifier potassium channel [1, 2]. Mutations of the *KCNH2* gene result in a disorder that is classified as a "channelopathy" as it involves control of the transmembrane movement of a cation. These channels are expressed in cells throughout the body, but are highly concentrated in the central nervous system (CNS) and the heart. In the CNS, the channel is involved in the normal regulation of neuronal function and cortical physiology, thereby explaining its pathologic role in epilepsy. Additionally, the proteins encoded by the *KCNH2* gene are involved in phases 2 and 3 of the cardiac action involving cardiac repolarization. Patients harboring this gene mutation may be at risk not only for seizures, but also abnormalities in cardiac repolarization leading to lethal arrhythmias. We present an 11-year-old girl with a *KCNH2* gene mutation who required general anesthesia for magnetic resonance imaging (MRI) as part of her evaluation for non-convulsive status epilepticus. End-organ involvement of *KCNH2* gene mutations and channelopathies are presented, previous reports of anesthetic care for these patients are reviewed, and options for anesthetic care are discussed.

Case Report

Investigations

We present an 11-year-old girl who presented for an MRI of the brain as part of the evaluation for non-convulsive status epilepticus. Her past medical history consisted of mild intellectual disability, autism spectrum disorder with accompanying intellectual impairment requiring substantial support (level 2), and attention-deficit hyperactivity disorder. She was in her usual state before presentation to the emergency department with abnormal head movements, blank stares and abnormal behavior. The symptoms used to occur every month for the last 1.5 years and tend to subside on their own. On that very day, her mother noted her sitting in abnormal body positioning and the symptoms continued to get worse. This was associated with fluctuating mental status throughout the day with acute worsening of grimacing, eyelid fluttering and urinary incontinence.

Diagnosis

A primary diagnosis of non-intractable absence epilepsy with

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status epilepticus was made based on electroencephalography (EEG). The EEG revealed occasional 1 second, diffuse spikes and poly-spikes with slow wave discharges. With the EEG findings being consistent with atypical absence epilepsy and her clinical presentation, treatment was started with ethosuximide and zonisamide. The co-existing autism and atypical absence epilepsy prompted further genetic testing and the decision to proceed with imaging including an MRI of the brain. Genetic workup revealed a mutation in the *KCNH2* gene and she was scheduled for an MRI of the brain under general anesthesia. The patient had no previous surgery or anesthetic exposure. Family history was negative for seizures, syncope, cardiac arrhythmias, or sudden/unexplained death.

Treatment

Preoperative evaluation for an MRI under anesthesia revealed an unremarkable physical exam and normal serum electrolytes, blood urea nitrogen, creatinine, complete blood count, and hepatic function. Due to the presence of the *KCNH2* mutation and hence the possible presence of abnormal *KCNH2*-encoded potassium channel resulting in both epilepsy and a predisposition to arrhythmias, consultation with cardiology was obtained and an electrocardiogram (ECG) was performed. The ECG was normal with a QTc of 424 ms (normal QTc for this age group being 370 - 450 ms). The patient was held *nil per os* for 6 h and was transported to the MRI induction room where standard American Society of Anesthesiologists monitors were placed. Inhalation induction was achieved with sevoflurane in 100% oxygen followed by placement of a 22-gauge peripheral intravenous catheter. Propofol (1 mg/kg) was administered intravenously and a size 2.5 laryngeal mask airway (LMA) was placed. Anesthesia was maintained with sevoflurane (inspired concentration 2-2.5%) in air and oxygen. Dexamethasone (0.1 mg/kg) was administered for prevention of postoperative nausea and vomiting. Vitals signs were stable throughout the MRI. Total intraoperative fluids included 300 mL of lactated Ringer's. After completion of the MRI, the LMA was removed. The patient was transferred to the post-anesthesia care unit. A repeat ECG was again normal with a QTc of 437 ms.

Follow-up and outcomes

The patient's postoperative course was unremarkable. She was discharged home with arrangement for cardiology follow-up. Her clinical course since discharge has been unremarkable with no further seizures.

Discussion

A channelopathy is as an inherited disorder caused by mutations in genes encoding for transmembrane ion channels, their subunits, or associated proteins. The ion channels regulate the transmembrane movement of cations including potassium, sodium, and calcium in various tissues throughout the body. They are highly concentrated in the CNS and the cardiac muscle and as such, their dysfunction can result in seizures and cardiac arrhythmias. The presence of these channels and their dysfunction in these two separate tissues explain the association of sudden death in patients with epilepsy syndromes as well as the occurrence of seizures in patients with repolarization defects and cardiac arrhythmias. These associations occur as primary pathologies in the separate systems rather a secondary occurrence following a primary event (seizures following cardiac arrest from an arrhythmia or seizures resulting in hypoxemia and cardiac arrest) [3-5].

Although identification of the number of genes known to cause ion channelopathies has increased over the past 30 years, three genes (*KCNQ1, KCNH2*, and *SCN5A*) account for the vast majority of patients with these disorders [6]. *KCNH2* gene mutation has been linked with various electrophysiologic alterations of repolarization including long QT syndrome (LQTS) type 2, brugada syndrome, and short QT syndrome [7, 8]. *KCNH2* gene mutations are also potentially linked to cerebral ion channelopathies, causing epilepsy, sudden arrhythmic death syndrome (SADS), and sudden unexpected death in epilepsy (SUDEP) [5, 6]. Therefore, epilepsy and these alterations in repolarization, manifesting as LQTS, may be unified under a single etiology, an ion channelopathy, manifesting in both the CNS and the heart.

During the perioperative care of patients with a *KCNH2* gene mutation, considerations may involve the associated seizure disorder as well as the potential for cardiac arrhythmias. Preoperative management to limit the potential for perioperative seizures includes optimizing and confirming therapeutic anticonvulsant levels prior to the surgical procedure. Routine anticonvulsant medications should be administered the morning of the procedure despite concerns of the patient's *nil per os* status with subsequent intraoperative dosing as needed [9]. Alternative routes of delivery may be required when enteral administration is not feasible during the perioperative period. When selecting specific agents for the induction and maintenance of anesthesia in patients with an underlying seizure disorder, there is limited evidence-based medicine [10, 11]. Although clinical seizure-like activity and even occasional spike and wave activity on the EEG has been reported with sevoflurane, these effects generally occur only when the inspired concentration is rapidly increased during anesthetic induction [12]. Specific agents such as etomidate or methohexital may activate the electroencephalogram and have the potential to augment seizure activity. However, in general, the inhalational and intravenous anesthetic agents including the barbiturates, benzodiazepines, propofol, ketamine, and the inhalational anesthetic agents are anticonvulsants and have been used to treat status epilepticus [10, 11, 13].

Cardiac involvement and clinical manifestations in patients with *KCNH2* gene mutation include sudden death or syncope related to cardiac arrhythmias including ventricular fibrillation or polymorphic ventricular tachycardia, predominantly due to LQTS. Patients with a family history of previous sudden unexplained death, syncope, or cardiac arrhythmias may require a more thorough cardiology evaluation prior to anesthetic care. In our patient, given the lack of a concerning

family history, and a normal QTc on the ECG, we decided to proceed with anesthetic care. QT prolongation can be acquired (related to metabolic disorders or medications) or originate from a genetic disorder (LQTS). The normal range of the QTc varies by age and gender, with the QTc being slightly longer in females. Prolonged QTc is defined as > 450 ms in males and > 460 ms in females. With increasingly longer QTc values, the probability of a patient having an LQTS-causing mutation increases as does the risk of lethal arrhythmias.Perioperative care of patients with a prolonged QT interval involves avoidance of medications and conditions that may further prolong the QT interval. Electrolyte imbalances including hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to anesthetic care.Furthermore, rapid access to the defibrillator is suggested and when clinically feasible, defibrillator pads should be placed prior to anesthetic care in patients with a prolonged QTc. In our patient, as we were providing anesthetic care for MRI, the defibrillator was located in zone 2 in the event that it was needed. The potential implications of various anesthetic agents (inhaled and intravenous) and recommendations for perioperative care in patients with a prolonged QT interval have been reviewed elsewhere [14, 15]. In our patient, we chose to keep intraoperative care relatively simple using sevoflurane and propofol. We chose not to use ondansetron for prophylaxis against postoperative nausea and vomiting given its potential impact on the QT interval. A repeat ECG was obtained, which revealed a normal QTc again, following anesthetic care prior to discharge home.

Learning points

The *KCNH2* gene encodes a protein component of the pore-forming subunit of a transmembrane potassium channel. This channel plays an essential role in phases 2 and 3 of the cardiac action potential involving cardiac repolarization as well as being expressed in various parts of the central nervous system where it regulates neuronal function. Mutations of the *KCNH2* gene result in a disorder that is classified as a "channelopathy". These channels are expressed in cells throughout the body, but are highly concentrated in the CNS and the heart. Patients harboring this gene mutation may be at risk for seizures and abnormalities in cardiac repolarization leading to lethal arrhythmias. Anesthetic care is impacted by the potential for both seizures and QTc prolongation. Anesthetic care should be tailored to avoid perioperative medications and scenarios that may increase the risk of seizures and further prolong the QTc.

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None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained from a parent for anesthetic care and potential publication. The patient information was de-identified for publication.

Author Contributions

AG performed the initial case review and manuscript preparation, literature review, and editing of subsequent revisions. AG and RB provided clinical care and reviewed the manuscript. JDT contributed to literature review, manuscript writing, and editing of the manuscript.

Data Availability

The data supporting the findings of this case report are available from the corresponding author upon reasonable request.

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