Author’s response to reviews

Title: Refractory ventricular fibrillations after surgical repair of atrial septal defects in a patient with CACNA1C gene mutations - Case report

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Author’s response to reviews:

Dear Prof Vipin Zamvar,

Thank you for the opportunity to submit revision of our manuscript “Refractory ventricular fibrillations after surgical repair of atrial septal defects in a patient with CACNA1C gene mutations - Case report” to your journal. We agreed with all reviewers’ comments and revised the manuscript point by point properly as follows.
Additional information on the CACNA1C mutation must be provided. Was the mutation novel or previously published? What is the variant ACMG classification? Is the variant seen in public exome databases such as ExAC or GnomAD?

Thank you for your all comments and suggestions to improve our manuscript. This mutation was novel, and this has not been published yet. Genetic analysis was performed in Shiga University of Medical Science, and a missense mutation, CACNA1C-K1580T, was identified. In this revised version, we added two co-authors, Dr Horie and Ohno, who performed genetic analysis. CACNA1C-K1580T is categorized into ‘likely pathogenic’ according to ACMG classification. This mutation is not reported in the exome database, ExAC, GnomAD, and Japanese genetic variation database (http://www.hgvd.genome.med.kyoto-u.ac.jp/index.html). Also, we added additional information about this mutation in row 4 of page 6 and Figure 3.

Was this variant identified in the family members that had reported arrhythmias?

Answer: The family members were diagnosed with long QT syndrome in other institutions, where the members have been treated and followed since diagnosis was made. The results and data of family members were not provided to us. Also, we did not analyze other family member in terms of gene screening.

Ref#5 is not first to associate CACNA1C in pathogenesis of LQTS (https://www.ncbi.nlm.nih.gov/pubmed/23677916). Additionally, mutations in CACNA1C have been associated with QT prolongation, cardiomyopathy and congenital heart defects. This should be referenced as well (https://www.ncbi.nlm.nih.gov/pubmed/26253506).

Answer: Thank you for your comments. We added the first reference of CACNA1C mutation in pathogenesis of LQTS at page 6. Also, the reference that you suggest us to cite is added to describe CACNA1C mutations relating to prolonged QT, cardiomyopathy and congenital heart defects at the first paragraph of discussion section at row 40 of page 6.

What are the post-operative risk in patients with LQTS and how do they relate to general risks after the procedures in this patient?
Answer: There are several factors which can prolong QT and trigger arrhythmic events before the induction of anesthesia and postoperative period of cardiac surgery in patients with long QT syndrome. Hypothermia after aortic surgery for brain protection is reported. And, hypokalemia induced by excessive diuretics can be seen after cardiac surgery and this condition can trigger events as well as the use of inotropes and postoperative pain. These factors can be avoided and possible drugs should be change to alternative ones in patients with long QT syndrome. In our case, sevoflurane, propofol, dopamine and dexmedetomidine were used for anesthesia and postoperative care, and these were categorized as possible cause of arrhythmic events or should be avoided in CredibleMeds (https://www.crediblemeds.org/). Therefore, if the diagnosis was made before the operation, these medicines would have been avoided and changed to other safe drugs. We added sentences to describe risk factors and information to provide proper perioperative care for patients with long QT syndrome at row 49 of page 6.

- Please provide normal values for potassium/magnesium. Reader now has to assume they were normal post-operatively. Also, what medications were used for anesthesia and post-operatively. Any of these risk for QT prolongation?

Answer: Thank you for your comments. Normal value for potassium was provided at row 29 of page 5. The value for magnesium was not measured during perioperative period, although that should have been checked to treat refractory Vf properly.

During the operation, sevoflurane, remifentanil, dexmedetomidine, propofol, fentanyl and Rocuronium were used for anesthesia. Cefazolin was used for prevention of surgical site infection. In the ICU, dopamine at 4mcg/kg/min and noradrenaline at 0.05 mcg/kg/min were administered for inotropic support. In addition, propofol and dexmedetomidine were given at the adequate level for sedation. Looking at the CredibleMeds, sevoflurane, propofol and dopamine are reported do not use for patients with congenital QT syndrome. Dexmedetomidine is also categorized as possible cause for arrhythmic events in patients with congenital long QT syndrome. These drugs should have been changed to alternative ones. We revised sentences properly thanks to your comments. Please have a look at row 55 of page 4, row 22 of page 5 and row 49 of page 6.

- Line 43: Fredericia should be Fridericia

Answer: Thank you for pointing out. We corrected the term properly.
Reviewer #2: The authors present a case of an adult with unrepaired CHD who had RBBB on preoperative EKG and a family history of rhythm disturbances on medications (the nature of which was not elucidated, nor was the treatment). The authors point out the importance of thorough investigation of both preoperative EKG findings and family medical history.

Minor Issue:

1. The authors might expand on how the patient's perioperative management would have changed if the diagnosis of long QT syndrome was made preoperatively

Answer: Thank you for your comments to allowed us to improve our manuscript. During the operation, sevoflurane, remifentanil, dexmedetomidine, propofol, fentanyl and Rocuronium were used for anesthesia. Cefazolin was used for prevention of surgical site infection. In the ICU, dopamine at 4mcg/kg/min and noradrenaline at 0.05 mcg/kg/min were administered for cardiac support. In addition, propofol and dexmedetomidine were given at the adequate level for sedation before the arrhythmic event. Looking at the CredibleMeds, sevoflurane, propofol and dopamine are reported do not use for patients with congenital QT syndrome. Dexmedetomidine is also categorized as possible cause for arrhythmic events in patients with congenital long QT syndrome. These drugs could have been avoided. Furthermore, careful induction and intubation before surgery could have been done under adequate sedation level after premedication. And, beta blockers could have been used after weaning from the CPB if hemodynamics was good. Maintenance of proper level of electrolytes such as potassium, calcium and magnesium could have been done. We revised sentences appropriately at row 55 of page 4, row 22 of page 5 and row 49 of page 6.

Again, thank you for this opportunity to submit revised version of our manuscript. I look forward to hearing from you.

Kind regards,

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