Author's response to reviews

Title: Synchronous cardiac arrest in monozygotic twins with hypertrophic cardiomyopathy - Is sudden cardiac death genetically pre-programmed?

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Author's response to reviews: see over
Re: Revision for case report “Synchronous cardiac arrest in monozygotic twins with hypertrophic cardiomyopathy - Is sudden cardiac death genetically pre-programmed?” (MS: 1244932965151527)

Dear Dr Shipley,

Thank you for the opportunity to address the reviewer’s feedback and provide a revised version of this manuscript. In the revised document, we have amended the case description and updated discussion with references as suggested. Overall it reads better with more clarity in the scientific material, and we thank the reviewer for that.

Further point-by-point response to the reviewer’s and editorial comments follows. Please do not hesitate to be in touch should you require any further clarification.

Yours Sincerely

Dr Muhammad Asrar ul Haq
**Reviewer's report:**

Comment: This report nicely illustrates a case of phenotypic overlap in a monozygotic HCM twin. Such a case with synchronous cardiac arrest has not been published before for as far as I know.

**Response:** Thank you!

**Minor essential revisions**

Comment 1: In both abstract and discussion it is mentioned that incidence of cardiac arrest in monozygotic twins is not known. Indeed it is not known, but should we expect it is any different from the incidence in non-twin HCM patients? Or do the authors mean that they have not heard of such an event in monozygotic twins, then do not use the term incidence and described it is not known from literature (as I happen to known cases, although not synchronous).

**Response 1:** Thank you for your comment. The abstract and discussion have been amended accordingly:

> "While various phenotypic features of HCM among monozygotic twin pairs are not uncommonly reported, occurrence of synchronous cardiac arrest among them is not known from literature."

Comment 2: I do not see any additional value of the first sentence of the third paragraph in the discussion section “While LGE in cardiac MRI...”. Can the authors explain why they mention this? Not one of the twin brothers has had an MRI.

**Response 2:** The above mentioned sentence has been deleted from our discussion.

Comment 3: On what basis was concluded that these men were monozygotic twins?

Response 3: This was established from the history taken from our patient and the deceased’s wife, and we do not have a scientific evidence for that. This has been now clarified in the manuscript as below. Thank you for pointing out.

> “Patient’s twin brother, in whom the basis of monozygosity was established by history taken from our patient, was diagnosed with HCM 30 years ago following a routine work-related medical check-up.”

**Major revisions**

Comment 4: In the discussion section the authors mention that the patient’s twin brother did not meet any of the established criteria for ICD insertion. May I remind the authors that both in the patient and the deceased twin brother risk stratification was incomplete, and that risk stratification (exercise test and Holter recording) is advised to be repeated on a yearly basis. It
can therefore not be said that risk stratification did not demonstrate an increased risk, just that it was not performed according to the guidelines (which might have cost a life.....).

Response 4: Thank you for the comment. The discussion has been amended accordingly, and the paragraph now reads:

“As SCD may be the only manifestation of patients with HCM, it is important to distinguish features of HCM, which are associated with high risk of SCD. The consensus document of American College of Cardiology Foundation and American Heart Association classified these risk factors as established risk markers and potential SCD risk modifiers(6). Established risk markers include previous cardiac arrest (ventricular fibrillation; VF) or sustained VT, family history of SCD at age < 50, unexplained syncope, abnormal exercise blood pressure, and LV thickness greater than 30mm (Table 1). The potential risk modifiers include presence of LVOT obstruction, LV apical aneurysm, late gadolinium enhancement (LGE) in cardiac magnetic resonance imaging (MRI) and high risk mutations. Furthermore, the guidelines recommend risk stratification be performed periodically every 12 to 24 months for patients with HCM who have not undergone an ICD implantation (Class IIa). Invasive electrophysiological study is not recommended in accessing SCD risk in HCM”

Comment 5: I do not understand why the authors mention on an underlying genetic factor responsible for timing of ventricular arrhythmias in a subset of patients with HCM (they mention this three times: abstract, discussion, and conclusion). If so I would like to have more information on why they think this could be the case here. Such a genetic factor seems very unlikely to me in this specific case. As monozygotic twins they already share the HCM causing mutation. We know that such mutations are associated with an extremely variable phenotype within families. An additional genetic factor most likely would also have been inherited from one of the parents, would it not have caused cardiac arrest in that parent or in another sibling? Perhaps not because it was transmitted by the parent not carrying the HCM mutation. If such a genetic factor would exist we would expect more reports of synchronous cardiac arrests in siblings/relatives in literature. I do not know this from literature and from my own experience with several hundreds of HCM families. We do know that a double mutations (on different alleles or in different genes) cause a more severe phenotype with earlier disease penetrance, more hypertrophy, and a higher risk of SCD. Why should an additional genetic timing factor be more likely than just coincidence? They are monozygotic and this is the VF is the only disease characteristic they have in common. Other parameters like LVH were different.

Response 5: Thank you for your comment. We have amended our abstract, discussion and conclusion.

1. It has been removed from the abstract which now reads:

‘Case Presentation:
We present a case of monozygotic twins with HCM who both had a cardiac arrest post physical exertion in 63rd year of their lives.
Conclusion:

This case highlights potential genetic predisposition of cardiac arrest in patients with HCM despite having different phenotypic expression. SCD may be the only manifestation of patients with HCM. Decision of ICD placement for primary prevention of SCD should be based on the recommended guidelines, clinical judgment and patient’s preference.”

Removed sentence from the abstract:

“While the occurrences of cardiac arrest between monozygotic twins may be coincidental, this synchronous timing may suggest an underlying genetic factor responsible for timing of ventricular arrhythmias in a subset of patients with HCM. “

2. The discussion has been amended:

“Our case report relates to twin brothers who had varying severity of asymmetrical LV hypertrophy, lived different life styles in two different geographical areas of Australia, and suffered cardiac arrest around the same time in their lives. This highlights the potential genetic predisposition of cardiac arrest in patients with HCM despite having different phenotypic expression. While it is likely to be a coincidence, the synchronous timing of cardiac arrest does raise a question whether an alternative explanation such as an underlying genetic cause could account for such synchronous timing. This however remains unlikely as lacks scientific evidence at this stage, and if such genetic factor did exist, more cases of synchronous cardiac arrests among siblings or relatives would have been reported in literature.”

3. This has been removed from the conclusion:

“While the occurrences of cardiac arrest between monozygotic twins may be coincidental, this synchronous timing may suggest an underlying genetic factor responsible for timing of ventricular arrhythmias in a subset of patients with HCM. “

The updated conclusion now reads:

“This case highlights potential genetic predisposition of cardiac arrest in patients with HCM despite having different phenotypic expression. SCD may be the only manifestation of patients with HCM. Decision of ICD placement for primary prevention of SCD should be based on the recommended guidelines, clinical judgment and patient’s preference. “

**Editorial comments/request:**

Comment 1: Please provide a consent statement that refers to both patients.

Response 1: The consent statement has been amended as follow:
“Written informed consent was obtained from our patient and also from the deceased’s wife for publication of this case report and any accompanying images. Copies of the written consents are available for review by the Editor of this journal.”

Comment 2: Please state in the Methods section whether written informed consent for participation in the study was obtained from participants or, where participants are children, a parent or guardian.

Response 2: As our manuscript is a case report not an original study, written consent was obtained only for publication of the manuscript.

Comment 3: *Title Page
Title page should contain, at minimum, the names, institutions, countries and email addresses of all authors, and the full postal address of the submitting author.

Response 3: The names, institutions, countries and email addresses of all authors, and the full postal address of the submitting author have been provided.

Comment 4: Please note that the <author names/author emails addresses> in your manuscript file differ from those entered in the submission system - please correct so they are consistent with each other.

Response 4: The authors’ names and emails are now corrected.

Comment 5: Please indicate clearly which affiliations should be linked to which authors, by way of numerical assignments, e.g.,
{Author name}1, {Author name}2,3
1. Institute, City, Country
2. Institute, City, Country
3. Institute, City, Country

Response 5: Affiliations have been labelled appropriately to the respective authors.

Comment 6: *Acknowledgements
By way of a section 'Acknowledgements?', please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation. Authors must describe the role of the funding body, if any, in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Please also acknowledge anyone who contributed materials essential for the study. If a language editor has made significant revision of the manuscript, we recommend that you acknowledge the editor by name, where possible. The role of a scientific (medical) writer must be included in the acknowledgements section, including their source(s) of funding. We suggest wording such as 'We thank Jane Doe who
provided medical writing services on behalf of XYZ Pharmaceuticals Ltd.'
Authors should obtain permission to acknowledge from all those mentioned in the
Acknowledgements section.

**Response 6:** All persons who are involved in the manuscript contributed equally and have been included in the authorship.