Peer-Review Record

Hypertrophic cardiomyopathy in *MYBPC3* carriers in aging

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Academic Editor: Ali J. Marian

Reviewer 1: Anonymous

Reviewer 2: Anonymous

Round 1

Reviewer 1 Report

This is a lengthy review on a timely subject of hypertrophic cardiomyopathy (HCM) caused by the MYBPC3 mutations in the elderly. HCM caused by mutations in the MYBPC3 phenotypically manifests at an older age in most cases and therefore, the topic is within the scope of the Journal.

The review, unfortunately, has a large number of shortcomings and requires attention of the senior authors who is well-recognized expert in the field. There are several erroneous statements and a large number of unclear ones. Overall, the writing style should be simplified, if not overhauled. The article does give the impression that it is written by someone who is not familiar let alone expert in the field, which contrast with the known expertise of the senior author. A round of revisions by the senior author who is expert in the field is required to will enhance clarity of the presentation and correct the incorrect statements.

Lines 23-24: “Elderly presentation of hypertrophic cardiomyopathy (HCM) is a well-known phenomenon in the familial inheritance of cardiac myosin-binding protein C3 (MYBPC3) gene variations.” The reviewer suggests revising: Hypertrophic cardiomyopathy (HCM) caused by mutations in the cardiac myosin-binding protein C3 (MYBPC3) gene typically manifests in the elderly.

Line 25: “pleiotropy”. This should be introduced before mentioning it here. The readers might not know what you mean here and how it relates to HCM caused by the MYBPC3.

Line 32: “However, aging compounds the pathophysiology to establish an even more severe form of HCM, as observed in asymptomatic MYBPC3 gene carriers.” It seems contradictory

in two points. First, please also note that mutation carriers, by definition, do not have a phenotype. Also the statement that "more severe form of HCM but asymptomatic …" is problematic. More severe form of HCM cannot be asymptomatic. Perhaps you mean severe hypertrophy in asymptomatic individuals.

Line 48: The reviewer suggests simplifying the sentences throughout the manuscript, as it gives the impression that it is written by someone who is not expert in the field (which is not the case for the senior author). For example, the following sentence could be simplified: "Among the hereditary cardiomyopathies, such as Mendelian (autosomal dominant or recessive), X-linked, and mitochondrial inheritance, hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) prevail." This could be changed to "hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) are the two most common forms of hereditary cardiomyopathies."

Line 53: "Gene carriers are at considerable risk of developing worse clinical symptoms compared to noncarriers." This is kind of self-evident, as non-carriers are not at the risk of HCM, unless something else is intended here.

Line 58: "Since the first clinical manifestation is death [1,4-6], it is important to understand the diagnostic potential of HCM-associated gene variants through genetic testing." The reviewer suggests revising as the first manifestation could be death but is not death in the vast majority of the patients with HCM. The sentence as written gives the impression that the first manifestation of HCM is death. This is the case only in a small minority of the cases.
Line 70: the definition needs a modifier and that is to add in the absence of a known cause of hypertrophy. Again, a revision by the senior authors will clean up the writing.

Line 72: "Abnormal loading, thinner walls, and hypertrophied myocardial fibers with disordered muscle bundles and interstitial fibrosis are some of the diagnostic features." This is perplexing! The authors define HCM in a previous sentence as an increased wall thickness but in the present sentence the authors describe "thinner walls"

Line 74: "High wall thickness" You mean thicker wall thickness, I assume.

Line 77: Apart from hypertrophy, HCM also displays prominent anomalies, such as remodeling of the left ventricle with progressive dilation and thinning of the wall that develops into HF simulating restrictive or dilated cardiomyopathy." The sentence is awkward and gives the wrong impression. The reviewer suggests revising to state that a subset of HCM evolves into DCM or RCM.

Line 111. "Genetic mutations in MYH7 and MYBPC3 genes are the most frequent causes of HCM." The word genetic is redundant, as you refer to genes in the sentence.

Line 114: "About 60% of HCM individuals are estimated to have sarcomere gene variants detectable in genetic testing" The yield of genetic testing is much lower. You may want to rephrase stating that 60% of the known mutations involve sarcomere genes or it is

estimated that 60% of HCM is caused by mutations in the genes encoding sarcomere proteins.

Line 121: “Among the 50 unique cardiomyopathy genes with truncating mutation, desmocollin2 (DSP), desmoglein (DSG2), plakophilin 2, Lamin A/C, titin (TTN), sodium voltage-gated channel, MYBPC3, troponin T (TNNT2) and phospholamban exhibit a high ratio of cases compared to reference populations for HCM[15]. The causal role of some of the genes mentioned in the list in HCM is not established. For example, truncating mutations in desmocollin 2 or plakophilin 2 are not known to cause HCM. This sentence is erroneous as it applies to HCM and should be revised.

Also regarding the above the gene symbol for desmocollin 2 is DSC2 and not DSP.

Line 125: “Genetic cardiomyopathies altering cardiac function are mostly truncating mutations harbored in the sarcomeric gene and, with less frequency, a nontruncating mutation.” This is incorrect as missense mutations are more common in HCM than the truncating mutation. The term “Genetic cardiomyopathies” is not proper here and should be changed to HCM.

Line 127: “Titin (TTN) and MYBPC3 are the most common gene mutations carrying a high odds ratio for HCM disease with a variable phenotype, including HCM and DCM [15- 18]”. Not sure what is meant here. The sentence does not make sense.

Line 129: “cMyBP-C and myosin alternate in the ratio of 1: 3 connecting thick and thin filaments. Along its N-terminal side, cMyBP-C binds to actin and myosin heads, whereas its C-terminal interacts with meromyosin and titin.” These two statements seem to be out of place. Need to be inserted somewhere else and expanded.

Line 134: “The age-dependent incomplete penetrance phenotype was largely observed among HCM patients in whom the major clinical manifestation is sudden cardiac death (SCD).” Change to: Phenotypic expression of HCM is age-dependent.

Line 137: references are not scanned.

Line 142: You may need to check the data and how the crude rate is calculated. (Fig 5 in the cited reference not explained so, see the definition of the crude rate in the method.). Crude rate does not mean much here. Age-adjusted mortality rate should be used.

Line 143: “Another follow- up study from the Sarcomeric Human Cardiomyopathy Registry observed higher mortality rates in HCM individuals compared to unaffected individuals of similar age [20]”. Please make sure you are extracting correct information here, as of course HCM patients have a higher mortality rate than unaffected individuals (or the general population).

This reviewer is stopping further comments and stopped reviewing the rest of the manuscript. The manuscript requires extensive revisions and rewriting by the senior author, before it is subjected to further reviews.

Author Response

We would like to express our gratitude to all the reviewers for their valuable comments and suggestions, which have significantly improved the clarity of our review. We have diligently addressed each of the reviewers' comments and thoroughly revised the entire manuscript. Therefore, we have decided not to provide a point-by-point response to the reviewers.

Notably, the senior author, **Dr. Sakthivel Sadayappan**, has made substantial edits to the article. Furthermore, we are pleased to announce the addition of a new senior co-author, **Dr. Julian Stelzer**, an established investigator in the field of cardiac myosin binding protein-C and hypertrophic cardiomyopathy. Dr. Julian Stelzer's expertise has greatly enhanced the quality of this review article. Please find our responses to the reviewers' concerns below, highlighted in blue font.

Reviewer 2 Report

Overall Summary: This review manuscript provides a comprehensive view on the presentation of hypertrophic cardiomyopathy in the aging population. It follows up on the observation that age-dependent incomplete penetrance of MYBPC3 gene mutations have heterogeneous clinically presentations primarily in elderly carriers, whereas younger individuals more frequently present with SCD. The topic is well suited to the Journal of Cardiovascular Aging. This is an important emerging topic and one that deserves focus. In this review potential pathogenic mechanisms are explored that could explain the presentation of HCM later in life and perhaps the manifestation of late-onset effects of gene variants. Variable penetrance provides a significant barrier when understanding pathological effects of various HCM MYBPC3 gene variants. The illustrations in the Figures are well down and convey important information about different aging mechanisms and how they can relate to late onset HCM. The review closes with discussion of how these underexplored mechanisms may provide an untapped repertoire of novel medical interventions to preserve cardiac function in late onset HCM patients.

Major Concerns:
1. The introduction should better introduce why MYPBC3 variants are being examined as a primary cause of late onset HCM.
2. The review contains a lot of important information but could be restructured to increase impact of the topics being covered. For example, there are long sections (paragraphs) defining common aging mechanisms, but then only a few sentences on how it could relate to HCM caused by MYBPC3 variants.
3. A suggestion for restructuring would be to focus on the aging mechanisms that have the strongest link with HCM and specifically the MYPBC3 variants and then cover topics with weaker or potential links. This would make the review easier to read.

4. The Section starting on Line 327 the section “Distribution of MYBPC3 Gene Variants in Elderly HCM Patient” is very important to the entire review. This information would be more digestible if this section was condensed and much of information on the MYBPC3 gene variants were included in a Table.
5. The Section starting on Line 411 “POTENTIAL MECHANISMS OF MYBPC3 VARIANTS CAUSING INCREASED SEVERITY WITH AGE” could be shortened. While important mechanisms are explained this entire section needs some streamlining. Adding a couple of the Tables containing the main points would increase the impact of what is being conveyed.

Minor Concerns:

1. Introduction – 1st sentence could be rewritten to make the intended meaning clearer.
2. Line 53 – please define gene carriers at first use, assuming you mean carriers of HCM variants.
3. Line 57-63 is the author discussing HCM in general or HCM caused by MYBPC3 pathogenic variants? This should be clarified.
4. Line 59 – the sentence starting with “Since the first clinical manifestation is death…” Needs to be revised or clarified, is the author intending to state that all MYBPC3 HCM variants first manifest with death?
5. In paragraph Lines 163-177 – The sentence is written “In addition to clinical features, genetic screening for the sarcomere gene was likely to be negative in elderly HCM patients” Can the authors further comment further on potential implications or reasons – e.g. is this because the patients diagnosed at an older age had sarcomeric mutations that had not previously been described as pathogenic? Younger individuals are more likely to manifest earlier because they harbor more severe mutations – and these variants are more likely to be labeled as pathogenic, whereas the other variants manifesting in aged individuals have been previously undetected?
6. In addition to clinical features, genetic screening for the sarcomere gene was likely to be negative in elderly HCM patients
7. Line 207 – please define acronyms at first use, e.g. BRG-1.
8. Line 362 – define burnout.

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