November 20, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14690_edited_final).

Title: Advanced Anderson-Fabry Disease Presenting with Left Ventricular Apical Aneurysm and Ventricular Tachycardia

Author: Marie-France Poulin, Alap Shah, Richard G Trohman, Christopher Madias

Name of Journal: *World Journal of Clinical Cases*

ESPS Manuscript NO: 14960

The manuscript has been improved according to the suggestions of reviewers:

1. The format has been updated as requested.

2. The name of the institutional review board (IRB) that reviewed this case was explicitly stated on the title page (Rush University Medical Center IRB). Please find attached to this revision a copy of the ethic waiver document.

3. A conflict-of-interest statement has been added to the title page. All authors have no conflict of interest to report relevant to this manuscript.

4. An informed consent statement was added to the title page: The patient gave her verbal informed consent prior to study inclusion.

5. The figure legends for Figures 3-5 were modified in order to be more comprehensive.

6. Revisions have been made according to the suggestions of the reviewers as follow:

Reviewer #1

(1) The authors should describe what is known about this mutation (R342Q) in the literature regarding pathogenicity. This mutation is present in the HGMD databank and some authors have already described it before and even checked its impact in functionality assays (Wu et al, Human Mutation 2011). Please cite and discuss these findings.

Thank you for this suggestion. The following sentence was added on page 5 in the second paragraph: "The R342Q mutation has been shown to lead to a complete loss of the GLA activity, and to be associated with a classical phenotypic presentation of AFD.[4,5]" References were also properly added to the manuscript.

(2) The authors should better describe Fabry disease in women. This is an important issue today due to the fact that women present later symptoms when compared to men and the difficulty to diagnose them.

Thank you for this suggestion. The following sentence was added on page 5 in the first paragraph: "Although the prevalence of AFD is likely underestimated, mutations are present in 1: 6000 to 1:40,000 females. Clinical manifestations in heterozygous females vary widely

from no apparent clinical disease to full expression of the disease.[2]" The following sentence was added on page 6 in the first paragraph: "In addition, women tend to present at a later age than men, and often only have milder symptoms, making the diagnosis of AFD more challenging in female patients." The references were properly added to the manuscript.

(3) It is not clear when the patient received the recombinant enzyme for the first time. Has the patient received regularly the treatment during this period? Which dose she received and how often? Was she followed during this time? How did the disease progress during this time? What was the ejection fraction of this patient two years ago?

The patient had been reluctant to initiate therapy until her symptoms worsened. She first received the enzyme replacement 18 months prior to this presentation. She had been compliant with the monthly infusion of 65 mg for one year, followed by an infusion of 60 mg every 2 weeks. Her EF was 75% two years prior, and her symptoms and overall disease progressed despite being on treatment (new TIA and worsening neuropathy and cutaneous lesions). This information was added to the manuscript on pages 4 and 5.

(4) Is the patient hypertensive? Has she any other cardiovascular complication?

Yes, the patient had a diagnosis of HTN and had been on lopressor and lisinopril for a few years prior to her presentation. Her blood pressure was well controlled. This information was added to page 5. She also was found to have lacunar infarct (cerebral vasculopathy) on an MRI that was done for headache and dizziness 18 months prior to presentation. This information was already mentioned on page 5.

(5) The authors should better contextualize hypertrophic cardiomyopathy.

In order to achieve this, we have contextualized AFD as follows on page 5, paragraph 1:
"Anderson-Fabry disease is a rare, X-linked lysosomal storage disorder caused by alpha-galactosidase A (GLA) enzyme deficiency, which results in an abnormal accumulation of sphingolipid catabolites in multiple organs, including the heart. Although the prevalence of AFD is likely underestimated, mutations are present in 1: 6000 to 1:40,000 females. Clinical manifestations in heterozygous females vary widely from no apparent clinical disease to full expression of the disease.[2]. Cardiac involvement can lead to myocardial hypertrophy, restrictive cardiomyopathy, coronary artery disease, arrhythmias (atrial and ventricular) as well as aortic and mitral valvulopathy.[3]"

We than conceptualized hypertrophic cardiomyopathy as follows on page 6, paragraph 2:
"In contrast to AFD, HCM is a relatively common genetic disease and is the most common cause of sudden cardiac death (SCD) in young people. Its estimated prevalence is 1 in 500. In HCM, the inheritance pattern is autosomal dominant. The mutant proteins that cause HCM are incorporated into intact filaments of the sarcomere and have been described as “poisonous peptides”. Local environmental factors such as pressure, the protein defect and modifier genes interact to induce the subsequent phenotype.[10] In HCM, development of ST elevation in leads V4 through V6 has been associated with LVAA formation.[11]"

(6) The text lack on important references regarding important issues like the ones cited before. Francisca Caetano et al, 2014 - Fabry disease presenting as apical left ventricular hypertrophy in a patient carrying the missense mutation R118C)

The authors had not seen this recent report. It is now briefly discussed on page 6 and 7 and

this reference was properly added to the manuscript.

Reviewer #2

General comments:

1. The formation of left ventricular apical aneurysm is quite rare in Fabry disease. Additionally, in female patients, the onset of symptoms is usually later compared with male patients. However, this patient presented with skin lesions, hypohydrosis and limb pain in her childhood. I wonder those findings including mid-ventricular obstruction are the characteristics of the R342Q misssense mutation in exon.

The R342Q missense has been associated with the "classical" phenotype of the disease, which includes all the symptoms that the patient had. This information was added to the text on page 5, with the proper reference.

2. The authors suggested a shared mechanism of LVAA formation in Fabry disease and HCM. Are there any previous reports suggesting a shared mechanism for LVH or apical aneurysm?

There are no such reports; this is a theory that the authors have suggested to explain the aneurysm formation. This was clarified on page 7.

Specific comments;

1. The 12-lead ECG after cardioversion should be exhibited as a figure.

An ECG that was performed after the cardioversion was added as Figure 2 and properly referenced in the text on page 4. The other figures were appropriately updated as Figure #3-7.

2. The patient manifested various symptoms which are typical for Fabry disease. I think enzyme replacement therapy should have been started earlier.

The authors agree with that statement. The patient only had been diagnosed a few years prior to her presentation after her brother tested positive for this genetic disorder. She was very reluctant to undergo therapy until her symptoms got worse, 2 years prior to presentation. This was explained briefly on page 5.

3. How is the involvement of kidney or central nervous system? I concern that apical aneurysm was caused by embolization due to atrial fibrillation. Was she treated with anticoagulation drugs?

Thank you for this comment. She had chronic atrial fibrillation and had been on anticoagulation with coumadin for years. This was discussed further on page 6. She was found to have lacunar infarct as mentioned in reviewer #1's comments. She had no renal involvement. This information was added on pages 5 and 7.

4. The first paragraph in page 5 should be cited at 'Case presentation'.

As suggested by the Editor, the first paragraph was cited as "Introduction".

Reviewer #3

Authors showed a case of AFD complicated by apical aneurysm and ventricular tachycardia. This report is written and presents well. Q1 12-lead ECG after termination of VT was not shown.

Thank you for this suggestion. The EKG was added as Figure 2 and properly referenced in the text on page 4.

Apical aneurysm developed at least during last 2 years. Serial ECGs should be presented. In HCM, ST-elevation in leads V4-6 often appears during the course of developing aneurysm.

Thank you for this suggestion. Serial EKGs from 4 years, 2 years, 1 year and 3 months prior are shown in a new Figure 6. Similarly to patients with HCM, new ST elevation in V4-V6 developed in our patient over this time period. This was discussed in the paper on page 6.

Q2 Apical aneurysm is associated with thrombus formation. In addition, the patient had atrial fibrillation. Was anticcoagulation therepy performed?

She had chronic atrial fibrillation and had been on anticoagulation with coumadin for years. This was discussed further on page 7.

Q3 Were antiarrhythmic drugs prescribed such as amiodarone or sotalol?

At the time of the VT, she received an intravenous bolus of amiodarone, which failed to break the VT. A DC cardioversion was performed shortly after. No other antiarrythmic medication was given. This information was added on page 4.

Reviewer #4

1. TITLE: The title is suitable and covers the correct data of the presented case. 2. ABSTRACT: The abstract is completely sufficient. 3. FIGURES: The data are very well presented in the figures. 4. PATIENTS, MATERIAL AND METHODS: The methodology part of the paper is clear and makes the case presentation understandable. 5. RESULTS ANS DISCUSSION The presentation and interpretation of the results is perfect. I congratulate the authors' team for diagnosis and presentation of the case.

Thank you for these nice comments!

3. References were updated as above.

Thank you again for considering our manuscript for publication in the *World Journal of Clinical Cases*.

Sincerely yours,

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