Author's response to reviews

Title: A classical phenotype of Anderson-Fabry disease in a female patient with intronic mutations of the GLA gene: a case report

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Author's response to reviews: see over
Dear Marinette Lacson and Prof. Ricardo J Gelpi,

Thanks for the assessment of our work. We are pleased that the reviewers found our paper interesting. We welcome their suggestions and have made the following changes in response to them. Furthermore, we have revised the format of our paper in accordance with the Journal’s style.

Referee 1 (Veroux):

1) The introduction should be reduced, focusing on the description of cardiac symptoms and genetical alterations of Fabry Disease, which is a well known genetic disease that do not require long description in the introduction section.

Response: done; the introduction has been reduced.

2) Was an enzyme replacement therapy considered in this patients? If yes, which ERT?

Response: done; please see the last 4 lines of the Case presentation section

3) Giving the clinical nature of the Journal, it could be useful to insert some data of the follow up of the patient, if available.

Response: done; please see the last 2 lines of the Case presentation section

4) the authors should better specified the originality of this case report, focusing in the rarity or significance of the atypical genetic variation and how this could reflect in clinical practice.

Response: due to the comments of referee 3, we have changed the title and the point of view of this case report, suggesting that a combined heterozygote intronic haplotype can be found even in patients with the classical form of FD. This is the originality of our case report. Regarding the impact on clinical practice, please see the last 6 lines of the Conclusions section.

Referee 2 (Gagliardi):

1. In the abstract please replace the phrase "Peculiar symptoms" with "Peculiar findings" or "Signs" since symptoms refers to what the patient feel and not to the findings in the biopsy.

Response: done

2. Figures footnotes are repeated.

Response: figure legends have been written again

3. In figure 1, it is necessary to use arrows to point out lysosomal inclusions and the inclusions in podocytes and mesangial cells.

Response: done
Referee 3 (Concolino):

1) There is an inconsistence in the title of the article “An Atypical Variant of Anderson-Fabry Disease in a Female Patient with Renal and Cardiac Involvement and Transient Ischemic Attack: a Case Report”. We can say that in this patient symptoms are not affecting a single, specific organ, like in the atypical forms of FD previously described, but the clinical manifestations are the expression of a multisystemic involvement that characterizes classical forms. The title of the manuscript could be modified. We suggest: “A classical phenotype of Anderson-Fabry Disease in a female patient with intronic mutations of GLA gene: case report”

Response: we have changed the title and the point of view of this case report, suggesting that a combined heterozygote intronic haplotype can be found even in patients with the classical form of FD.

2) Regarding the Abstract form, I would change:
   a. Case presentation: delete “proteinuria”
   b. Conclusions: 1) “symptoms” should be replaced by “findings”; 2) The sentences “In our patient clinical picture showed a multisystemic involvement with early onset of symptoms, thus suggesting that these polymorphisms can be found even in patients with classical form of FD” could be added.

Response: a) done; b1) in accordance with referee 2’s comment, we have replaced “symptoms” with “findings”; b2) done

3) Regarding the Background section:
   a. Line 5 “damaging normal cellular functioning” should be replaced by “with consequent cellular damage”
   b. Line 10 the other cellular types in which Gb3 accumulation occurs could be added
   c. Line 17 “In the latter study, 86% had an intronic mutation, called c.936+919G>A, that is associated with an atypical form of FD which is characterized by residual enzyme activity that remains high enough to prevent organ damage in childhood and adolescence.” Add the reference
   d. Line 19 it’s not clear what does “severe skin involvement in the teen years” mean.
   e. Line 2 from bottom “In this patient the evidence of occasional.....” should be replaced with “In this patient molecular evaluations confirmed the diagnosis of FD: we found four mutations in promoter and regulatory intronic regions of the GLA gene.”

Response: a) done; b) we deleted the sentence to which reference is made; c) done; d) we replaced “in the teen years” with “in adolescence”; e) we changed the entire sentence, in accordance with the new point of view of the report (please see the last 4 lines of the Background section)

4) Regarding Case presentation section:
   a) everything is clear and detailed, but I think that too much space is spent to describe renal biopsy and cardiac MRI study.
   b) What found in these instrumental exams, is obviously specific for FD, but not less important than other clinical manifestations. For this reason at line 49 I’d add: “As a result of the renal biopsy and cardiac MRI study findings, associated to the clinical history, suggesting FD, the patient underwent...”
Response: a) only 8 lines (21-28 in the Case presentation section) are dedicated to the description of renal biopsy; as for the description of cardiac studies, we think that a detailed report is necessary given the nature of the Journal and the severity of findings; b) done

5) Regarding Conclusions section:
   a) Line 1 I suggest to modified the first sentence in this way: “In this paper we reported the case of a female patient in which, clinical history and specific instrumental findings suggested the diagnosis of FD. A genetic survey....”
   b) Line 5 the sentences “These mutations have been observed in several patients with atypical variants of FD characterized by not severe clinical picture, with symptoms affecting a single, specific organ, and which manifests later in life because residual enzyme activity remains high enough to prevent organ damage in childhood and adolescence. In our patient multisystemic involvement and early onset of symptoms seems to suggest a classical form of FD, but without any mutation in coding region of GLA gene. Our results....” should be added
   c) Line 5 from bottom The sentences “We do......Variant of FD.” Should be replaced by “This can lead to confirm diagnosis of FD in a higher number of patients, thus providing a more realistic evaluation of the prevalence of FD in general population.”

Response: a) done; b) done (please see lines 5-11 in the Conclusions section); c) done (please see the last 3 lines of the Conclusions section)

Referee 4 (Pineiro):

Review references and the way of citation

Response: done

We hope that these changes have sufficiently addressed the reviewers’ concerns and will make our manuscript acceptable for publication.

With kind regards,

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