Author's response to reviews

Title: De Toni-Debre-Fanconi syndrome in a patient with Kearns-Sayre Syndrome. Diagnostic delay in one case

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Author's response to reviews:

Cover letter giving a point-by-point response to the concerns

I agree with many aspects. Please, see the author’s answers below:

Reviewer: Sebastian Beck
Comments to authors:

GENERAL:

(1) This is an interesting case report about a patient, who presents a genetic disorder (KSS) and developed some additional symptoms (that have been seen sporadically in other patients already. The authors underline that awareness for these symptoms is important for everybody who treats patients with KSS.

Author's reply:
Mitochondrial myopathies have many different faces, with a complex array of symptoms. Some symptoms can be so mild that they’re hardly noticeable, while others are life-threatening. The possibility of mitochondrial dysfunction needs to be taken into account by every medical subspecialty.

(2) The introduction and case presentation is clear in general. The pathophysiological thoughts about mitochondrial disease in the discussion would be appropriately placed in the introduction.

Author's reply:
I agree with this. I placed in the introduction the general aspects about the mitochondrial myopathies.

(3) Pictures of Brain CT and/or MRI would be nice, such as histological pictures
from muscle biopsy.

Author's reply:
We do not have the pictures, we do have the written descriptions. I could provide brain CT pictures but I am afraid that they do not have a good quality.

(4) Figures 1, 2, and 4 do not add much information; Figure 3 is still doubtful in terms of maintaining the confidentiality of the patient. Even with obtained informed consent from the patient’s parents.

Author's reply:
Showing the first picture, we tried to emphasize that as an infant, our patient wasn’t affected yet by the disease. It looked like a normal developed infant. In the pictures 2 and 3 we wanted to show the progression of palpebral ptosis. We know that the patient could be recognized by other people, but his parents stated that they signed the informed consent and there is no problem if their child is recognized, they will be happy to help the practitioners around the world to see the clinical presentation and to read the description.

We will do the comments to the pictures. We will add audiogram’s picture, genetic testing written result.

CONTENT:
(1) In the discussion the authors mention that they found 8 references for Fanconi syndrome in KSS. As this association is the key message of the article, it would be worth while citing all of these references.

Author's reply:
We already added these references to bibliography, as you suggested.

(2) The first paragraph of the conclusion is no conclusion derived from the case presentation or from the discussion.

Author's reply:
I agree, and we changed this aspect.

(3) Figure 4: The patient with KSS seems to be the patient on the right in the picture, not on the left.

Author's reply:
I agree with this comment. We changed the interpretation of this picture.

FORMAL:
References should be cited in the sentences, not after the sentences, example: “The possibility of mitochondrial dysfunction needs to be taken into account by
every medical subspecialty. [4]"
Should be: “The possibility of mitochondrial dysfunction needs to be taken into account by every medical subspecialty [4].”

Author's reply:
I agree. We changed and we placed the reference’s number in the sentence.

Spelling errors should be eliminated (some examples: “rethinopathy”, “establishe”, “sterted”).

Author's reply:
I agree and we tried to eliminate all the spelling errors.

REFERENCES:
References have not been prepared carefully according to the instructions for authors; “[CrossRef]”, “[ISI]”, “[Medline]” or “[PubMed - indexed for MEDLINE]” should be taken out.

Author's reply:
I agree, we changed this aspect as you could see in text.

Quality of written English: Needs some language corrections before being Published

Author's reply:
I agree and we tried to do the language corrections.

Declaration of competing interests:
I declare that I have no competing interests.

Author's reply:
I agree. In the new manuscript, we mentioned the declaration of competing interests.

Reviewer: Marek Niedziela

Comments to authors:
General comment: This case report on Kearns-Sayre syndrome, a rare genetic disorder, is a descriptive article with unfortunately no new findings, ideas. The title is focused on the insulin dependent diabetes mellitus but in fact the main conclusion is that it is worthy to screen for the Toni-Debre-Fanconi Syndrome. This makes the reader somehow confused. I would say that rather patients with the Toni-Debre-Fanconi should be suspected maybe for Kearns-Sayre syndrome
and such a conclusion would be of greater importance for practitioners.

Author's reply:
I agree with these comments, but the title was focused on the insulin dependent diabetes, because the diagnosis was established when he developed diabetes and we consider this aspect very important for the physicians treating children with diabetes (or young adults). Also, we considered your comment very good and useful and we changed the title according to this suggestion.

Detailed comments: Introduction and discussion are rather poor. If the diagnosis is so easy why this patient was not diagnosed for such many years!

Author's reply:
We do not consider the introduction and discussion “poor”. We agree, the diagnosis could be easy to made (based on clinical description and laboratory tests), but doctors are usually not aware about this possibility (KSS syndrome, and de Toni-Debre-Fanconi preceding the Kearns-Sayre syndrome). KSS is a rare diagnosis in clinical practice and the main point of this article is that the internists and sub specialists are in a pivotal position to recognize and treat these diseases (Mitochondrial-DNA mutations-related diseases).

The molecular aspects were not properly described. In the OMIM base there is no one gene described in which the deletions occur but it is a base with a total description of the disease and the review of the literature (see introduction).
There is no one gene in which deletions occur in KSS as proposed in this paper.

Author's reply:
There is no one gene in which deletions occur in KSS. In the first manuscript it was an error, indeed, concerning this aspect and we do not mention this aspect in the new manuscript.

There is no any lab test attached in the form e.g. of table. If authors do not show the deletion they should not state it was detected!

Author's reply:
We provided a copy of the genetic testing written result.

The picture of the patient is really typical in terms of short stature, ptosis, neuromuscular problems. However authors are only descriptive - only ECG was provided.

Author's reply:
Unfortunately, we do not have the MRI images, we only have the written descriptions of MRI, as well as from the muscle biopsy. We'll provide some
pictures with brain CT but they do not have a good quality. It is very important to be descriptive, because we always have in mind the importance of clinical diagnosis! Starting from this point, we could order laboratory tests etc. In countries such as ours, sometimes it is very hard to have all you need and you could take in account this aspect! Probably there are many countries around the world were such rare and difficult diagnosis are made mainly on the clinical basis, thanks to many dedicated doctors that do not have access to the high tech.

Quality of written English: Needs some language corrections before being Published

Author's reply:
I agree. We tried to made the corrections in the new manuscript.

Declaration of competing interests:
'I declare that I have no competing interests'

Author's reply:
I agree. We mentioned this aspect in the new manuscript.