Author’s response to reviews

Title: Mucopolysaccharidosis Type VI: Case Report with First Neonatal Presentation with Ascites Fetalis and Rapidly Progressive Cardiac Manifestation

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Version: 1 Date: 25 Oct 2019

Author’s response to reviews:

São Paulo, SP, BRAZIL

October 9th, 2019

Dear Editorial Board of BMC Medical Genetics,

Please find below the answers to the reviewers’ comments of the manuscript “Mucopolysaccharidosis Type VI: Presentation with Ascites Fetalis and Rapidly Progressive Cardiac Manifestation”.

Eirini Manoli (Reviewer 1): The manuscript by Rachel Sayuri Honjo et al, "Mucopolysaccharidosis type VI: Case report with first neonatal presentation with ascites and rapidly progressive cardiac manifestation” describes a rare presentation of prenatal fetal hydrops in MPS type VI associated with rapidly progressive mitral valve insufficiency and congestive heart failure by 6-7 months of age necessitating valve replacement at age 1yr. Successful resolution of the cardiac failure and improved growth and only mild motor delays are reported at age 2.5yrs with enzyme replacement therapy initiated after the cardiac surgery. The case is novel and expands the spectrum of MPS disorders that can present with non-immune fetal hydrops,
highlighting the need for LSD work-up in "idiopathic" cases to facilitate early diagnosis, genetic counseling and referral for early intervention/enzyme replacement.

Infantile onset mitral valve insufficiency/cardiomyopathy have been previously described in MPS VI patients. It would be helpful to the readers and more directly relevant with this case report if these cases were discussed in more detail and contrasted to the current case. They could be described in a separate table on the early onset cardiomyopathy in MPS VI, and include the case by Fong L.V. et al, 1987 (PMID: 3109796), presenting as endocardial fibroelastosis without valve involvement. Given all previous reports precede molecular testing, the current manuscript is also important for facilitating possible future genotype-phenotype associations.

ANSWER: The case reported by Fong et al. was added in the discussion. Also, we could identify one case of fetal hydrops (Choy et al., 2015) who eventually was diagnosed with MPS VI at 13 months of age and added in the reference and in the text. However, this case did not have molecular investigation.

Addressing the following comments would add to the clarity of the report:

* Clarify the fetal hydrops monitoring and resolution during pregnancy. Did it resolve spontaneously, was there any follow up of hydrocephalus or echocardiogram after birth?

ANSWER: Medical record was reviewed and there was an initial misunderstanding – the patient has hydrocele only, and not hydrocephalus. OFC was normal at birth and so was the cranial US. The text was corrected accordingly.

* Was there hepatosplenomegaly, macrocephaly at birth/ the first few months? Why was a skeletal survey performed at 1 month of age?

ANSWER: At birth, OFC was normal and it was noted a unilateral clubfoot. Skeletal survey was indicated to evaluate any skeletal malformations but it was performed only at 1 month of age. There were no signs of hepato or splenomegaly (and abdominal ultrasound was normal at birth).

* Provide more details on LV shortening fraction at 7, 9 and 10 months, and response to therapy and comment on any cardiac conduction anomalies. A normal ejection fraction is described in Fig 4, with no details on the age of the patient

ANSWER: LV shortening fraction at 7, 9, 10 and 11 months were 70%, 56%, 79% and 58%, respectively. ECG showed left ventricular overload and normal sinus rhythm. This piece of information was added in the text, after the decision on the cardiac surgery at 11 months.

Figure 4 shows the Echocardiogram at the age 9.5 months (information added in the legend).

* If available, provide glucosaminoglycans at diagnosis (only values after enzyme replacement are mentioned).
ANSWER: Urinary glycosaminoglycans at diagnosis in the normal upper limit – 402 µg/mg Cr; with dermatan sulfate excretion. This information was added to the text.

* Comment more on need for earlier detection and enzyme replacement.

ANSWER: As suggested by the other Reviewer, a sentence regarding Newborn Screening and early ERT initiation was added at the end of Conclusions section.

* Provide the change at the protein level and discuss genotype-phenotype associations of cardiac variants.

ANSWER: The change at the protein level was cited and genotype-phenotype associations were commented, even though the articles focused more in the general phenotype, and not only the cardiac one. Our patient’s variants are related to classical MPS VI and not with the non-classical cardiac phenotype.


ANSWER: The references were added and the last sentences of Conclusions was changed to: “Fetal hydrops has been detected in patients with MPS I, IVA and VII. The present case indicated that, in MPS with neonatal presentation, including fetal hydrops, clinicians should include MPS VI in the differential diagnosis.”

Alia Ahmed, M.D. , C.C.R.P. (Reviewer 2): In case presentation, could you elaborate about the patient’s presentation at birth. It would be helpful for the readers if authors organized patient's presentation as a timeline or systematically mention according to the months from 1 month to 11 months (or the time of surgical intervention).

ANSWER: The only sentence that was out of the timeline is the one related to the X-ray results. Thus, the sentence “Skeletal survey performed at one-month-old, due to congenital clubfoot and dysmorphisms, revealed mild proximal misshapen metacarpals and thickening of the provisional cartilage” was moved to the beginning of the case report.

On page 10, line 238, authors mentioned, "although it was well known that ERT does not prevent cardiac glycosaminoglycan deposits." Stabilization of valvular disease has been observed in some patients (Braunlin et al. 2011). Stabilization or even a slower deterioration may be suggested a favorable contribution for the rapidly growing or in case of progressive nature of MPS VI (Scarpa et al. 2009).
The sentence was deleted and in discussion another was added: “Some authors show stabilization or slower deterioration of valvular disease with ERT. In our patient, an early diagnosis was also important, because even though the cardiac disease was surgically assessed, other manifestations of MPS can be treated by ERT.” New references were added.

Regarding page 6, line 147: in case of severe form or rapidly progressing disease where the symptoms may be present at birth, usually diagnosis gets sooner than between the 2nd and 3rd birthdays.

ANSWER: The text was corrected as suggested.

At the end of the conclusion, on page 11, after line 269, authors may acknowledge about the prospect or the importance of the newborn screening (NBS) which can lead to early diagnosis and treatment for MPS VI. If ERT can start within first few months of life after diagnosis may prevent cardiac valves involvement (Braunlin et al. 2011)

ANSWER: The following sentence was added at the end of Conclusion: “Newborn screening can lead in the future to early diagnosis of MPS, making it possible to start ERT within the first months of age, which may prevent cardiac valve involvement and other MPS manifestations.”

Sincerely yours,

Rachel Sayuri Honjo on behalf of the authors

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