Author’s response to reviews

Title: Short Stature as a Presenting Symptom of Attenuated Mucopolysaccharidosis Type I: Case Study and Clinical Insights

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Author’s response to reviews:

15 October 2018 James Mockridge, PhD Editor

BMC Endocrine Disorders

Re: BEND-D-18-00230

Dear Dr. Mockridge:

We are pleased to submit our revised manuscript “Awareness of Short Stature as a Presenting Symptom of Mucopolysaccharidosis Type I Can Lead to Early Identification of Patients” for consideration of publication in BMC Endocrine Disorders as a case study.

We thank the reviewers for their careful and thoughtful review, and have addressed each of their comments below. NOTE The additional editorial/technical requests sent 20 October 2018 have been made.

Thank you in advance for your consideration of our revised paper; we look forward to hearing from you.

Sincerely,
1. Please move the Abbreviations to just above the Declarations.
RESPONSE: Edit Made

2. Please rename the "Conclusions and Clinical Insights" heading in the Abstract to "Conclusions". RESPONSE: Edit made

3. Please reformat Table 1 to be an editable table, currently it is just a list of bullet points. Another option would be to incorporate the information into the manuscript and not include this as a table. Should you choose this option, please ensure you amend the citations and table numbering throughout.
RESPONSE: Table 1 is now an editable table

4. Please clarify the age of the patient in the Consent for publication section, if the patient was under 18 when seen by the clinicians, was parental/guardian consent obtained? Patients must be 18 years old and over in order to Consent for Publication themselves. If parental consent was obtained, please confirm whether this was verbal or written. If the patient was 18, please disregard the points regarding parental consent. RESPONSE: text has been modified to read: “The patient, who was over 18 at the time of manuscript preparation, provided written consent for use of data in the publication.”

5. Please remove the second "Conclusions" heading next to the last paragraph. RESPONSE: edit made

6. At this stage, please remove the CARE checklist. We thank you for including this, it was instrumental to the review process, but is no longer needed at this stage. RESPONSE: removed

7. At this stage, please upload your manuscript as a single, final, clean version that does not contain any tracked changes, comments, highlights, strikethroughs or text in different colours.
All relevant tables/figures/additional files should also be clean versions. Figures (and additional files) should remain uploaded as separate files. RESPONSE: completed

ORIGINAL comments

Technical Comments:

Please correct the heading of 'Data Sharing' to 'Availability of data and materials'.

RESPONSE: Edit has been made to the declarations section on page 11.

Reviewer comments:

Motomichi Kosuga (Reviewer 1):

Because this paper is mainly targeted at pediatric endocrinologists, authors should emphasize the need of careful observation in evaluating bone age. Bone deformity of MPS generally begins from the infancy. When a patient with MPSI is referred to endocrinologists, dysostosis multiplex including metacarpal pointings and bullet shaped phalanges has already presented. Therefore, it is important not to overlook the presence of hand bone deformity when evaluating bone age.

RESPONSE: This excellent point made by the reviewer, that a pediatric endocrinologist ordering bone-age X-rays would become aware of the classic phalangeal abnormalities of MPS dysostosis multiplex, has been added to the discussion on page 7, line 13: “It is important to note that assessment of bone age in children with growth delay is typically done with an X-ray of the left hand and wrist; thus, pediatric endocrinologists are ideally situated to identify early phalangeal abnormalities (i.e., bullet shaped phalanges) typical of MPS I.”

On page 7, line 38, authors mentioned the results of the uGAG test indicated in Figure 4. However figure 4 was not attached in this paper.

RESPONSE: The text should refer to Figure 3, and the edit has been made.

Minor revise: On page 1, MPS I is an abbreviation of mucopolysaccharidosis type I.

RESPONSE: The edit has been made in the list of abbreviations.

Alia Ahmed, M.D., CCRP (Reviewer 2):

According to author's comment in the discussion and conclusions section, page 8 between lines 14 to 16, Juvenile idiopathic arthritis was the most common incorrect diagnosis made. Then why
not MPS screening may start from the rheumatologist or orthopedist? Why author is emphasizing only on endocrinologist?

RESPONSE: We appreciate that the reviewer is asking for clarification of this important point. We do point out in the discussion that information in references 38 (now 40) and 39 (now 41) is available for pediatric rheumatologists for help in differentiating JIA from MPS I. However, endocrinologists/growth specialists also encounter individuals with MPS prior to diagnosis, and may not always recognize signs, as indicated in references 35 (now 37) and 36 (now 38). We have more clearly laid out the rationale/need for awareness among pediatric endocrinologists with the revised text on page 8 lines 12-17:

“While algorithms exist that include MPS I in the differential diagnosis of juvenile arthritis for pediatric rheumatologists [40,41], growth specialists and endocrinologists may be among the physicians encountering individuals with undiagnosed MPS disorders, and similar guidelines could prove helpful for recognizing the red-flag signs and symptoms of MPS I and other MPS disorders. A proposed algorithm that includes short stature as a presenting sign in attenuated MPS I has recently been published [45].”

Don't you think to emphasize on newborn screening (NBS) awareness is more important than anything else? Do you have any comments on NBS?

RESPONSE: We agree with the reviewer that NBS is a vital tool for early diagnosis of individuals with MPS disorders. We have added this text to the introduction section on page 3 last paragraph to page 4 first paragraph. “While pilot NBS programs for MPS I are in progress around the world (see new reference 27) the diagnostic delay persists, and there has been no significant improvement in reducing the delay in diagnosis of MPS I as of 2017 (see new ref 28). Thus, it remains likely that children with undiagnosed MPS I will be referred to specialists, including endocrinologists, for their care, and awareness of early clinical signs and symptoms remains important.”

Heather Church (Reviewer 3):

Figure 3 describes a recommended diagnostic algorithm for MPS disorders. The urine GAG screen states that the urine analysis may be qualitative or quantitative. Quantitative analysis may be a full GAG analysis by TMS but may also purely be an assessment of total GAGs. It is well documented that total GAGs may not be raised in attenuated MPS patients and could give a false negative result if this test is performed in isolation. It is important to stress that a thorough urine MPS screen is required either by total GAGs and electrophoresis, or by TMS.

RESPONSE: We thank the reviewer for the comment, and have amended the figure (added to second footnote: “GAG may not be elevated in individuals with attenuated disease, therefore electrophoresis or tandem mass spectroscopy may be needed to look for abnormal GAG pattern” and text on page 7, line 19-21 (“Upon consideration of an MPS disorder, a urine GAG (uGAG)
test (that may include analyses to determine abnormal GAG pattern such as electrophoresis or tandem mass spectrometry) can determine the presence of lysosomal storage material.”) to reflect the stringency that may be needed for uGAG screening.

Figure 3 - Enzyme function test states DBS as source and screen for treatable MPS subtypes (MPS I, II, IV and VI). Please also consider MPS VII.

RESPONSE: Information added to Figure 3.

The manuscript states that variants in the IDUA gene have been identified but doesn't state what the genotype is. This is useful information.

RESPONSE: We agree that this is useful information for the reader. The individual had the following pathogenic missense variants, c.1148G>A (p.R383H) and c.1598C>G (p.P533R), and we now include this information in the results section on page 6, second paragraph, line 8.

General comment - the focus of this paper is MPS I but there is considerable clinical overlap with other MPS disorders. The discussion describes how MPS I should be part of a differential diagnosis in short stature but this is equally be true of other MPS disorders, particularly MPS II, IV, VI and VII. The discussion would benefit from a broader angle to encourage the target audience to consider MPS disorders in general and not focus on MPS I.

RESPONSE: This is an important point that we do make in Figure 3, which recognizes the overlap in presenting signs across MPS disorders. We have added a sentence on page 7, line 14 that “There is considerable overlap of presenting symptoms among the MPS disorders, therefore, screening identified in Figure 3 should take into account other MPS disorders where short stature is common.” The existing text in the discussion and in Figure 3 already used the broader term MPS disorder when discussing uGAG, enzyme, and genetic testing.