Author’s response to reviews

Title: Splicing analysis of CYP11B1 mutation in a family affected with 11β-hydroxylase deficiency: case report

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Author’s response to reviews:

April 15, 2016
Dr. Michael O'Reilly
Editor-in-Chief
BMC Endocrine Disorders

Dear Dr. O'Reilly,

Thank you for your email of April 05 indicating that our manuscript: BEND-D-16-00038 entitled “Splicing analysis of CYP11B1 mutation in a family affected with 11β-hydroxylase deficiency: case report” will be acceptable for publication once some minor points have been addressed. We
offer the following clarifications and changes in response to the reviewers’ comments (provided in courier new 11 point type).

Reviewer 1

Comments:

In this manuscript, the authors identify and describe two previously reported mutations in the CYP11B1 gene that result in a severe form of CAH. Whilst neither mutations are novel, this is the first report of their combined compound heterozygous presentation with additional insight provided into their functional significance via the minigene analysis of the IVS7+1G>A mutation that confirms full skipping of exon 7-8 of the CYP11B1 gene. The study is scientifically sound and the manuscript is well written. Despite the lack of novelty regarding the mutations, this study adds additional insight into the field, that this reviewer feels justifies it's inclusion within this respected journal.

We thank the Reviewer for his interest in our work.

Minor comments 1:

The authors should clearly state within the abstract that these mutations are previously reported. This is covered within the main body of the text but should be expanded to the abstract so as not to mislead.

Ans:

As suggested by the reviewer, we have added “Although the identified mutations have been previously described, this is, to our knowledge, the first report of these mutations in compound heterozygotes” in the abstract, page 2, line 34-35.

Minor comments 2:

Introduction, line 96, masculinization should read Masculinization?
We thank the reviewer for the correction of misspelled word.

Reviewer 2

Comments:

This paper describes the phenotype of two siblings with 11β-OHD. The phenotype is that of classic 11β-OHD. They have performed functional studies which give more information on the pathogenic mechanism of disease in the IVS7+1G>A mutations. In general there are many grammatical errors (some highlighted below) and the paper does not always read fluently. The phenotype description could be shortened.

We thank the reviewer for pointing out some errors. We have corrected some grammatical errors and revised the manuscript as the reviewer suggested.

Abstract:

Line 31 A 46,XX sister-amend to read A 46,XX female. Line 32: her 46,XY brother presented with sexual precocity-change to precocious puberty The abstract does not flow that well. Move sentence regarding mutation analysis (line 38) to after the line on Sanger sequencing (line 34). Conclusion: Unexciting-could be improved

We have made a revision as suggested by the reviewer (highlighted in yellow).

Main paper:

Line 58-sexual precocity-change to precocious puberty. Line 62-cosyntropin-ACTH stimulation
We have made a correction as suggested.

Line 78-At that time-what time

We have revised the sentence to be clearer (Page 4, line 78-79).

Lines 83-87-put all information into a table with baseline and stimulated values. This will be much clearer and reduce length of text.

We have made a revision and added Table 1 as suggested by the reviewer.

Line 86-change levels to concentrations (on all occasions)

We have made a correction as suggested.

Line 91-after molecularly confirmed diagnosis-Treatment should be started on the basis of no response to ACTH stimulation

We have made a correction as suggested.

Line 95-what is musculinization (precocious puberty). Was hypertension not identified when the patient presented as opposed to the patient presenting with hypertension.

We have made a revision to make it clearer.

Line 99-height gain accelerated-describe as change in growth velocity centile/height SDS.
We have added a change in height SDS as suggested by the reviewer.

Was urine steroid profile performed?

No.

Lines 169-171-repeat of introduction

We have deleted the statement as suggested by the reviewer.

Line 177-at 2 years old not in infancy

We wrote “Blood pressure is usually normal during infancy and hypertension is often identified later in toddlerhood or in childhood, although its presence in infancy was demonstrated”

We cited the reference 12 (Eur J Pediatr. 1985 Jan;143(3):231-3) which showed the unusual case with 11 beta-hydroxylase deficiency in whom the hypertension was found at birth.

Abstract

A female newborn infant with ambiguous genitalia was found to have hypertension (121/82 mm Hg) immediately after birth. The plasma testosterone (T) (0.73 nmol/l), delta 4-androstenedione (delta 4-A) (5.9 nmol/l), dehydroepiandrosterone (DHEA) (8.9 nmol/l), as well as 17 OH-hydroxyprogesterone (17 OHP) (152 nmol/l) were elevated. The diagnosis of 11 beta-hydroxylase deficiency was finally established on the basis of elevated plasma eleven-deoxycortisol (compound S) (greater than 0.6 mumol/l) and confirmed by the normalisation of the blood pressure during hydrocortisone therapy. Our case is probably the youngest patient with 11 beta-hydroxylase deficiency in whom the hypertension was found at birth.
Lines 209-211-rewrite as message not clear but would be the main point of getting this data published.

We have revised the discussion for better understanding (page 10, line 208-210).

Editorial Requests

Ethics:

If your study involves humans, human data or animals, then your article should contain an ethics statement which includes the name of the committee that approved your study.

Consent:

If your article is a prospective study involving human participants then your article should include a statement detailing consent for participation.

If individual clinical data is presented in your article, then you must clarify whether consent for publication of these data was obtained.

We have provided the ethics statement on page 10, line 217-221.

Availability of supporting data:

BioMed Central strongly encourages all data sets on which the conclusions of the paper rely be either deposited in publicly available repositories (where available and appropriate) or presented in the main papers or additional supporting files, in machine-readable format whenever possible. Authors must include an Availability of Data and Materials section in their article detailing where the data supporting their findings can be found. The Accession Numbers of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript must be provided and include the corresponding database name.
We have already provided these data in the manuscript.

Authors Contributions:

Your 'Authors Contributions' section must detail the individual contribution for each individual author listed on your manuscript.

We have provided the data of 'Authors Contributions' on page 11, line 225-228.

We thank the reviewers and editors for their enthusiasm for our work. We really appreciate all your comments and trust that the revised manuscript will now be acceptable for publication in “BMC Endocrine Disorders”.

Sincerely,
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