Author’s response to reviews

Title: Spontaneous Fertility and Variable Spectrum of Reproductive Phenotype in a Family with Adult-Onset X-Linked Adrenal Insufficiency Harboring a Novel DAX-1/NR0B1 Mutation

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Author’s response to reviews:

January 16th 2020
Da Li, M.D., Ph.D.
BMC Endocrine Disorders

Dear Dr. Da Li

We are very thankful to the editor and reviewers for the opportunity to revise our manuscript to BMC Endocrine Disorders. It is now presented fully revised, entitled: "Spontaneous Fertility and Variable Spectrum of Reproductive Phenotype in a Family with Adult-Onset X-Linked Adrenal Insufficiency Harboring a Novel DAX-1/NR0B1 Mutation" (BEND-D-19-00514) by Cerutti et al.
We appreciate the thoughtful critiques from Endocrine Disorders reviewers and found their questions and suggestions helpful. We have addressed all raised concerns and also corrected them in the manuscript highlighted in yellow to facilitate appreciation. We hope that all the changes we have made are acceptable to their concerns.

We look forward to hearing from the acceptance of our revised manuscript for publication in BMC Endocrine Disorders.

Best regards,

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Replying point by point

Reviewer reports:

Aldo Ferreira-Hermosillo, MD, MSc (Reviewer 1): The authors present three cases of X-linked adrenal insufficiency due a novel mutation in DAX-1. The cases are well documented, and the background and discussion section have enough information for supporting their diagnosis.

I have only three minor comments:
1) In the abstract section. The term "sibling" is commonly used to refer to brothers or sisters. In this case series, they are relatives due just two cases are siblings.

Reply: Thanks for all the positive and kind comments. We have changed the term “sibling” to the correct “relatives” in the abstract and throughout the text.

2) In order to improve the case report, I suggest adding the CT images demonstrating the adrenal hypoplasia (if available).

Reply: We appreciate your suggestion for improving our manuscript and added an adrenal CT available only for the index case (III.5) as Figure 2: The contrast-enhanced computerized tomography scan demonstrating bilateral adrenal hypoplasia from the DAX-1 mutated index patient.

3) For the second case (male of 64 years) please specify how does the hypergonadotropic hypogonadism was diagnosed? Did he have some symptoms?

Reply: We are thankful to the reviewer for the opportunity to add this information regarding hypogonadism from the second familial case (index's uncle) in the manuscript. The maternal index's uncle had complained about hypogonadal symptoms such as erectile dysfunction, decreased libido, and depression six years before PAI diagnosis. Unfortunately, he has declined any additional lab investigation or therapy during this period. Therefore, we include in the text more information in this regard as follows "Six years before PAI diagnosis was complaining about hypogonadism symptoms (e.g., low libido and erectile dysfunction), but he has declined any additional medical investigation."

Emilio Fiore (Reviewer 2): In this work the authors report a novel DAX-1/NR0B1 mutation in members of a family affected by late onset X linked adrenal hypoplasia congenital (AHC). They describe a very late onset form of AHC with variable hypogonadal and reproductive features including spontaneous fertility observed in two members of the family. For this reason the authors suggest that NR0B1 mutation carriers, even those that are allegedly asymptomatic, should be carefully monitored, with periodical exams, including spermograms and early sperm banks in order to warrant fertility preservation on AHC males and diagnose very late primary adrenocortical insufficiency.

Reply: We are thankful to the reviewer for the opportunity to correct the manuscript and prevent misleading regarding its title. We agree with the reviewer that our manuscript is a family report rather than a case report. We wonder the board could reconsider it as a family report.
Comments

a) Figure 1A is a low resolution image and it is not clear.

Reply: We appreciate the critique and have provided a new Figure 1A with a better resolution in the revised version of the manuscript.

b) How many members of this family (both males and females) were tested to rule out primary adrenocortical insufficiency?

Reply: Thanks for reminding us about clarifying this matter. In 5 (all males)/7 deceased family members, we were able to retrieve some clinical signs of adrenocortical insufficiency. In these cases, we believe they might have died due to hypocortisolism, as depicted in figure 1A legend as (.). However, unfortunately, their serum cortisol has never been appropriately registered since these cases were outside the university hospital. Three DAX1-mutant affected family members had documented primary adrenal insufficiency. Besides, by the time of writing this manuscript, a questionnaire was performed to all alive family members (including females), and no other primary adrenal insufficiency or pubertal alteration signs and symptoms were observed. While performing genetic counseling, we reviewed features of hypocortisolism and hypogonadism, and so far, no other symptoms have arisen. As observed in our DAX-1 family, other families reported in the literature have shown affected males with delayed puberty or even adrenal insufficiency in female carriers (Seminara et al., 1999, Bernard 2006).

c) Was any case of delayed puberty described in this family?

Reply: We understand the concern, but as far as we were able to retrieve from the family history, there was no history of delayed puberty. We included one statement about this concern in the discussion as follows: “Additionally, there was no history of delayed puberty or clear PAI symptoms in alive family members, including in female one (III.7). Indeed, some female carriers of DAX1 mutation have been reported presenting with puberty delay (Bernard P, Ludbrook L, Mol Genet Metab. 2006;88:272–9/ Seminara SB J Clin Endocrinol Metab 1999, 84(12):4501-4509). This intriguing clinical manifestation may reflect variable gene expression or even oligogenicity in female carriers, similarly to other X- linked diseases (Sykiotis et al., 2010). J Clin Endocrinol Metab. 2010;95:3019–27)".