PM PEDIATRIC MEDICINE
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Peer Review File

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Reviewer 1

General Comments:

This manuscript is well written, with updated information on etiologies of primary adrenal insufficiency.

Reply: Thank you for your time in reviewing our submission and offering feedback.

Specific Comments:

Comment 1. Page 10, line 222. Correct "Enteropathy"

Reply 1: The error on my screen is on line 206, in the paragraph on MIRAGE syndrome. We have corrected this spelling error.

Comment 2. Page 19, Line 426. Please clarify the dose for infants or young children.

Reply 2: We have changed the wording of this section to make the individual dosing guidelines for children >=2 years of age, <2 years of age, and infants more clear.

Comment 3. Page 20, Line 455. I do not think serum cortisol is checked for monitoring while patients are on glucocorticoids.

Reply 3: Thank you and we agree with your comment and changed it.

Comment 4. Page 39, it might be easier and practical to add dose in ml/kg for dextrose in 10% for pediatric patients.

Reply 4: Thank you for this suggestion, the table has been updated to this notation.

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Reviewer 2

General Comments:

This is a review of primary adrenal insufficiency (PAI), with an emphasis on genetic causes of PAI, many of which present in the newborn or pediatric population. The review addresses much of the same general material that is covered in the 2016 Endocrine Society Guideline on diagnosis and treatment of PAI in adults.

The less usual, genetic causes of PAI are especially relevant to the pediatric population. There are several recently published reviews of these less usual genetic causes of PAI in the literature, some of which are cited in this manuscript by Ergun-Longmire et al, although some relevant articles have been published since the authors concluded their literature search.

The present review doesn't fully address some of the basic questions: What are the clinical manifestations of PAI in children, how are they distinct from adults, and how frequent are the rare genetic etiologies by age group? What clinical and laboratory assessments may be undertaken to distinguish etiologies for the important genetic syndromes associated with PAI? Who should be tested for genetic causes, and what genetic tests may be recommended? How are less severe genetic abnormalities of above conditions expressed later childhood or adolescence?

In the current manuscript, treatment of these elements was somewhat superficial and non-systematic. I am suggesting some additional details and data citations may be included that would strengthen paper and also distinguish it from the other recent reviews.

In general, I felt that statements relating to results of specific studies were not adequately referenced.

If I understand this review correctly, based on journal and content of this manuscript, the focus is on PAI in pediatric population. However, that is not specified in the title or introduction.

Reply: Thank you for your suggestion. We added "pediatric population" to the title and in the text when it was appropriate.

Specific Comments:

Comment 1. The Endocrine Society Guideline recommends that etiology for PAI be established in all cases, and Figure 1 in that Guideline covers various diagnostic considerations including x-21 hydroxylase antibodies, congenital adrenal hyperplasia, VLCFA, adrenal imaging etc. Introduction mentions: In infants and children, however, genetic causes, especially steroidogenic enzyme defects known as CAH, are the most common cause of PAI. It would be helpful if the authors would provide additional information concerning the etiologies of PAI by age. In addition, it would be helpful the spectrum of age of presentation and clinical presentation of the genetic disorders, since they are not restricted to newborns. Which patients should have

genetic testing if usual causes (Figure 1 in Endo Society guideline) have been excluded? Where are the genetic tests available for suspected cases?

Reply 1: Thank you for your comment. We have added a number of references and statements to the paper in order to more rigorously address this comment from the reviewer. We have also created a figure based on the data collected in order to visually illustrate the added information. High index of suspicion is crucial for the diagnosis and genetic testing should be added when it is appropriate.

Comment 2. Along these lines, not much use is made of Table 1, it is merely a listing. Please expand this table to include the genetic loci that are sequenced to establish diagnosis. Also recommend highlight the disorders that are typically screened in contemporary Next-Generation sequencing (NGS) panels, and what percent of the rare genetic disorders are captured using this methodology. Also include mode of inheritance information.

Reply 2: We thank the reviewer for the suggestion and have removed Table and created a replacement table of syndromes, genes, and loci for this paper (Table 1).

Comment 3. Recommend expanding discussion of expected clinical and laboratory findings. For example, is ACTH elevation and hyperpigmentation characteristic of all the disorders discussed? Distinguish mineralocorticoid status in 11-hydroxylase and 17-hydroxylase deficiencies.

Reply 3: We have added additional information about clinical and laboratory findings to many of the listed disorders. We have decided to omit more detailed discussion of enzyme-specific manifestations of CAH from the paper due to the wide variety of literature available on this topic.

Comment 4. Although implied by the term ‘familial glucocorticoid deficiency’, please discuss aldosterone secretion in these disorders. Also specify whether these conditions are associated with salt-wasting and if they require mineralocorticoid replacement.

Reply 4: We have added a statement and reference to the paper about the usual lack of impact of FGD on the RAAS.

Comment 5. Please review source material and revise as appropriate information for age of onset of adrenal hypofunction associated with DAX mutations. I think it is an oversimplification and inaccurate to state that in these patients present with adrenal insufficiency that they may present with salt loss in either early infancy or at one year of age (bimodal distribution). Recommend inclusion of additional information about DAX mutations, provide the reader with some explanation of the association of DAX mutations with hypogonadtrophic hypogonadism and additional discussion of late onset of manifestations of partial DAX mutations, expected sequence of endocrine abnormalities, etc. In discussion of bimodal age of presentation, authors mention neonatal vs. one year of age. This is an oversimplification, please revise. Please include additional discussion of DAX mutations generally that will help the clinician recognize the spectrum of these disorders in pediatric population.

Reply 5: The reviewer asks for a more detailed explanation of age of onset in patients with DAX mutations & the spectrum of associated disorders across the lifespan. We have added the previously mentioned figure to help delineate age of onset in various discussed disorders. We thank the reviewer for pointing out the inaccurate statement regarding the bimodal distribution of DAX-related symptom onset and have reworded the section & added references for increased accuracy. We have also added some guidance for clinicians in terms of optimal patient population that should be tested for DAX1 mutation.

Comment 6. The paper discusses the importance of hypoglycemia as a presenting manifestation of childhood hypoadrenalism. Other literature also mentions ketotic hypoglycemia in DAX mutations, for example. Please comment and discuss ketotic hypoglycemia in PAI, including pathophysiology and clinical and diagnostic relevance.

Reply 6: All patients with adrenal insufficiency may have ketotic hypoglycemia due to impaired gluconeogenesis and glycogenesis.

Comment 7. Please specify extra-adrenal manifestations that distinguish FGD types 1 and 2.

Reply 7: Added a reference for extra-adrenal features.

Comment 8. Can you include a table showing etiologies of PAI in children by age and by study, as in Camtosun et al (J Clin Res Pediatr Endocrinol 2021;13(1):88-99). Similarly, would it be possible to include a table of clinical manifestations and their frequency, as in above or Hiseh & White (J Clin Endocrinol Metab 96: E925–E928, 2011). Also consider incorporating matrix related age of onset and specific genetic mutation to associated clinical manifestations, as illustrated in Buonocore et al Journal of the Endocrine Society, 2021, Vol. 5, No. 8, 1–15 (see Figure 5 for example). It would probably make sense to include Contosun and Buonocore information and references in your revision.

Reply 8: We thank the reviewer for this suggestion and have created a figure showing various etiologies of PAI and related manifestations along the lifespan.

Comment 9. As hyperpigmentation is one of the most common presenting manifestations, please discuss its relevance in pediatric population, including pathophysiology related MCR1.

Reply 9: Thank you for the recommendation. We have added discussion of the etiology of hyperpigmentation to the beginning of the paper, as well as the role of *MC1R*.

Comment 10. Table 2 is entirely generic and could be written just as well for adult endocrine population. As example, there is no mention of seizures, hypoglycemia, or ketotic hypoglycemia anywhere in clinical manifestations section (Table 2). So I am recommending revision of the tables be revised to be more focused on pediatric population and rare causes of PAI in particular. Note in Table 2 that

'hypopigmentation' is listed, I believe hyperpigmentation is intended here, please correct.

Reply 10: Thank you for your comment. We corrected "hypopigmentation" and have added signs and symptoms specific to children and infants.

Comment 11. Similarly, Table 3 was generic and of limited clinical use. This table could be expanded to include recommended monitoring for dose adjustments. If possible, include information about which disorders do or do not require mineralocorticoid replacement therapy.

Reply 11: Thank you for your comment. We have added The Endocrine Society Recommendations for dose adjustments in the text.

Comment 12. In discussion of corticosteroid replacement therapy options, it may be preferable to give dosing guidance; the statement that longer acting glucocorticoids such as prednisone or prednisolone may be substituted but at a reduced dose compared to hydrocortisone dose is rather general.

Reply 12: Thank you for your suggestion. We have added longer acting glucocorticoids and the specific dose recommendations in the text.

Comment 13. The authors may consider include discussion of testicular adrenal rest tumors in CAH and other forms of PAI.

Reply 13: Thank you for this suggestion. We have not included this in the manuscript due to length considerations.