

Peer Review File

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Reviewer A

1. Please list home medications and antihypertensive medications used during his admission. Various anti-hypertensive medications affect renin and aldosterone levels, therefore it is imperative to list all medications. OTC med such as Biotin can cause abnormal thyroid assays mimicking thyrotoxicosis. Please clarify whether the patient was using Biotin before the thyroid assays performed.

RE: Thank you for reviewing the manuscript and raising this concern. We provide the following explanation for your question:

According to the patient's self-reported medical history, there was no special discomfort in the past, and he had not had regular health checkups, and was not found to have elevated blood pressure, nor had he taken any medication.

(Page5-6 Line79-81)

And the patient was not taking biotin, and biotin-containing beverages and dietary supplements and nutraceuticals before the thyroid test.

2. Past medical history not listed. Does he have a prior history of hypertension

RE: Thank you very much for your advice, and I agree that presenting the patient's past history is necessary. Although the patient had not been previously found to have elevated blood pressure, after the patient is admitted to the hospital, ophthalmic fundus examination indicated arteriovenous tortuosity in both eyes, artery thinning, and the presence of binocular arteriosclerosis. The abnormal parameters indicated target organ manifestations of hypertension. The patient has a history of hypertension without knowing it and has had it for some time.

(Page7 Line115-119)

3. Page 6. please stated the rationale for “alkali supplementations” instead of the more commonly accepted volume expansion with isotonic saline for rhabdomyolysis especially in the

RE: Thank you for your careful reading of my manuscript, and in response to the questions you raised ,our answers to your questions are as follows.

The 2020 Clinical Consensus of the American Board of Critical Care in Trauma Surgery suggests that the two most commonly cited fluids used for this resuscitation are lactated Ringer’s solution and saline (0.9% or 0.45%).(PMID:32944457)

The use of sodium bicarbonate to deter the development of AKI in rhabdomyolysis is currently controversial. Some studies (such as PMID: 23324509 PMID: 6696564 PMID: 19571284) propose that patients benefit from sodium bicarbonate

infusions .An acidic urine environment potentiates myoglobin-induced renal toxicity. The basis behind the use of sodium bicarbonate is that it promotes alkalization of the urine and counteracts the process of heme pigment precipitation, thereby decreasing the direct pigment injury. Urine alkalization is also useful in diminishing redox cycling and lipid peroxidation, thus preventing oxidative stress, tubular damage, and renal vasoconstriction. Hence, it is believed that urine alkalization, optimizing the pH higher than 6.5, can prevent renal impairment. These are the reasons why we chose alkali supplementations to curing this patient.

4. in my opinion, the neurologic exam, echo, and doppler findings are too detailed. Simply summarizing pertinent findings can make the manuscript more succinct

RE: Thank you very much for the reviewer's comments, we agree with you very much and we have revised the manuscript where you mentioned that the examination was too detailed, keeping only the positive signs. We have changed “Neurological examination of patients with normal cerebral nerves, normal muscle nutrition, no involuntary movements, no muscle bundle tremor .The muscle strength of the four limbs was decreased; The joints can move on their own when the upper limbs fight against gravity but cannot fight against resistance; when the muscles of both lower limbs contract, they contract but cannot drive the joints to move; the muscle strength of the upper limbs is grade 3; the muscle strength of both lower limbs is grade 1, and the muscle tone was decreased. Normal depth and superficial sensation, negative sensory separation sign, negative Romberg's sign. The reflexes of the two brachial tendons and triceps tendon were normal, the reflexes of the knee and Achilles tendon were weakened, and the Babinski sign was negative bilaterally.” to “Neurological: the examination of the four limbs muscle strength is weakened, upper limb muscle strength grade 3, bilateral lower limb muscle strength grade 1, muscle tone is not abnormal, bilateral biceps and triceps tendon reflexes are normal, bilateral knee and Achilles tendon reflexes are weakened. Cardiac ultrasound showed that the left atrium of the heart was large and the left ventricular wall was thickened with small amount of regurgitation of the aortic valve and tricuspid valve, and the rest of the cardiac ultrasound did not show any obvious abnormalities.” in the manuscript.

(Page 6 Line86-91)

5. Page 7. What is your interpretation of elevated Angiotensin II level in the setting of PA? Both renin and angiotensin II levels should be suppressed in PA

RE:Thanks for your question, in response to the question you posed, we think the following may be helpful in answering this question.

In general the changes in renin, angiotensin II and aldosterone in PA are characterized by high aldosterone and low renin and angiotensin II. However, when thyroid hormone levels are elevated, renin-angiotensin system activity is markedly increased. Some studies (PMID: 31396276) have suggested that plasma renin, angiotensin II and aldosterone are higher in hyperthyroid patients than in normal subjects.

Some studies(PMID:7000394) have suggested that angiotensin II levels are reduced in hypothyroid patients compared to healthy individuals.

The elevated angiotensin II level in this PA patient is considered to be due to the exposure to increased thyroid hormone levels, which is one of the special features of this case.

6. page 7 line 131 What is decubenus test?

RE: Thank you for reviewing my manuscript so carefully. I'm sorry for the mistakes you mentioned,I apologize for the confusion due to my poor writing. I have carefully checked and revised it.

page line “the decubenus test was performed, and the result remained positive” corrected as “Repeat the measurement of the RAAS system and calculate the ARR ratio results remained positive.”

(Page8 Line 141-142)

7. Page 7 it is difficult to follow the confirmation test performed. Please write the detailed protocol and results

RE: Thanks for your question. Because this patient is unique, we conducted a detailed investigation before finally confirming the diagnosis, and the following is the detailed process of clarifying the diagnosis of this patient.

Considering the association between potassium loss and the renal pathway, the adrenal function was evaluated through RAAS system (standing position).

	K+	Renin pg/ml	Angiotensin II pg/ml	Aldosterone pg/ml	Cortisol ng/dL	ACTH ng/L	ARR
standing position	3.67	2.32	167.77	178.90	9.16	19.33	7.71

The levels of aldosterone and renin were determined by an automated chemiluminescence immunoassay. According to the guideline In accordance with the 2008 American Endocrine Society guidelines for the treatment of primary aldosteronism published in the journal JCEM, the ARR cut points (3.8, 5.7, and 7.7) in different centers, patients screened positive and required further confirmatory testing to demonstrate; blood cortisol and ACTH rhythms:

	8: 00	0: 00
Cortisol ng/dL	9.16	2.93
ACTH ng/L	19.33	10.23

The test was positive, but interference by stress and other factors cannot be ruled out.Repeat the measurement of the RAAS system and calculate the ARR ratio :

	K+	Renin	Angiotensin	Aldosterone	Cortisol	ACTH	ARR
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		pg/ml	II pg/ml	pg/ml	ng/dL	ng/L	
Supine position	-	1.74	127.76	163.49	13.33	26.97	9.40
standing position	3.93	1.88	147.19	158.35	7.21	18.54	8.40

The ARR ratio reaches the screening cutoff for primary aldosteronism and the aldosterone level decreases in the standing position, consider the possibility of an aldosterone tumor; perform a captopril test to confirm the diagnosis.

	8: 00	0: 00
Cortisol ng/dL	13.33	1.41
ACTH ng/L	26.97	5.30

Rhythm present and cortisol level <1.8ug/dl at 0:00 sleep, 24 hr urinary cortisol: 37.8nmol/24H. Insufficient basis for hypercortisolism.

captopril test :

	K+	Renin pg/ml	Angiotensin II pg/ml	Aldosterone pg/ml
pre-drug	3.85	2.55	179.46	245.24
One hour after taking the drug	-	2.33	182.46	196.22
2 hours after taking the drug	-	2.62	177.42	211.93

Although the aldosterone level decreased after taking the drug, the inhibition rate was 20% (1 hour), 13.6% (2 hours); support the diagnosis of primary aldosteronism; adrenal CT (plain scan): right adrenal adenoma (right adrenal gland can be seen in the right adrenal gland, rounded low-density shadow, with clear margins, the size of about 17 * 11mm); at present, combined with its functional test and imaging, support the diagnosis of primary aldosteronism. Hyperplasia is diagnosed and staged as a right adrenal adenoma.

	adrenaline	norepinephrine	dopamine
plasma	35.63	160.86	55.64
urine	5.59	51.71	319.23

Blood and urine catecholamine hormones are within the normal range, not supporting pheochromocytoma and paraganglioma.

8. Page 8 Since the patient is > 35 y/o, was adrenal even sampling done before resection of adrenal adenoma? The presence of adenoma doesn't necessarily exclude the possibility that aldosterone secretion might be from unilateral or bilateral adrenal hyperplasia undetected by CT or microscopic adenoma in the contralateral adrenal gland.

RE: We feel great thanks for your professional review work on our article. According to your nice question here are my answers.

Published in 2021 in Lancet Diabetes Endocrinol The Clinical Consensus of the Diagnosis and treatment of primary aldosteronism(PMID: 34798068) suggests that CT and adrenal venous sampling (AVS) are currently recommended in the guidelines for the diagnostic work-up of patients with PA. Adrenal CT is the first step for primary aldosteronism subtype evaluation and should be done in every patient. AVS currently remains the gold standard for subtyping and is recommended by all guidelines and consensus statements, Adrenal biopsy was not chosen. This guidelines clearly state that unilateral adrenalectomy can be performed without AVS when the patient is <35 years of age and combines spontaneous hypokalemia with marked aldosteronism and when adrenal CT has shown a unilateral adenoma.

A clinical prediction score to diagnose unilateral primary aldosteronism (PMID: 22918872) and Hypertension with or without adrenal hyperplasia due to different inherited mutations in the potassium channel KCNJ5(PMID: 22308486)

expert consensus on bilateral adrenal vein blood collection suggests that AVS is not feasible in the following cases: (1) young PA patients (<40 years old) with typical symptoms who have clearly demonstrated unilateral adenoma on imaging; (2) patients who refuse to undergo surgery or who are at high risk of undergoing surgery; (3) PA patients with suspected adrenal gland malignancy on imaging; and (4) patients with familial hereditary PA that is clearly type I or type III on genetic testing.

This case patient was a 38 year old young PA patient with typical symptoms and an imaging presentation of a unilateral adenoma, According to these guidelines, there is no absolute indication for AVS testing, so we went straight to surgery for the patient.

9. what is procaldehydes (line 177), phaldehydes (line 210) , and primary aldehyde (page 17 line 257)

RE: Thanks to the reviewer for carefully reviewing our work and pointing out this mistake. I apologize for the error that has crept in while preparing the manuscript. I acknowledge that the spelling of procaldehydes should be corrected to primary aldosteronism. I have revised all.

(page 10 line 186-187) (page 12 line 216) (page 14 line 264)

10. The discussion section needs to be more coherent and is too long for a case in my mind. It should clearly outline the take-home messages from the case. In my opinion, hypokalemia leading to rhabdomyolysis is not that uncommon and per se probably does not warrant a case report however thyrotoxicosis associated with rhabdomyolysis is more interesting and unique

RE: Thank you very much for your comments, a detailed literature review has resulted in more content and length. We have streamlined the manuscript somewhat.

Reviewer B

1. All abbreviations in the **abstract, main text/figures/tables and legends** should be defined when they are first used.

In addition, please check through the abstract and the main text to ensure the correctness of the full names of the abbreviations. Such as **Primary hyperaldosteronism (PA)**.

Full names of the abbreviations in figures should be defined in the legend.

Full names of the abbreviations in tables should be defined in the tables' footnotes.

RE: Thank you for carefully reading our manuscript, and we have made the following changes to the issues you raised. All abbreviations in the abstract, main text/figures/tables and legends were defined at the time of first use and added to the manuscript.

(Page 4 Line 64) (Page 19 Line 407-412) (Page 22 Line 434-435)

(Page 23 Line 479-480) (Page 25 Line 497)

2. Please reduce the key words to five.

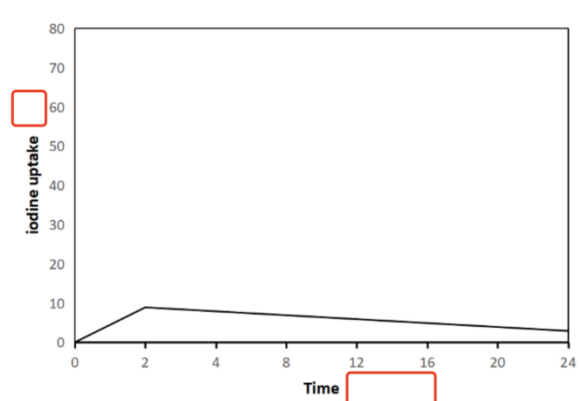
RE: As per your request we have reduced the keywords to 5.

Keywords: Primary hyperaldosteronism; Thyrotoxicosis; Rhabdomyolysis; Hypokalemia; Case report

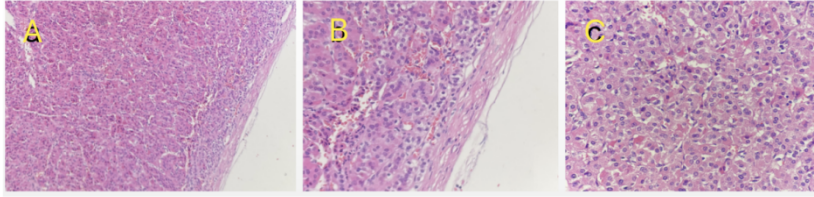
(Page 3 Line 52)

3. Figure

- 1) Please add a unit to the X-axis and a percentage to the Y-axis in Figure 1.

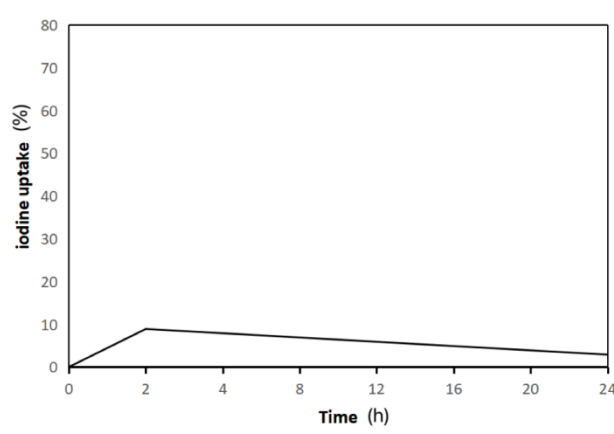


- 2) Please use capital letters to number the images in Figure 5.



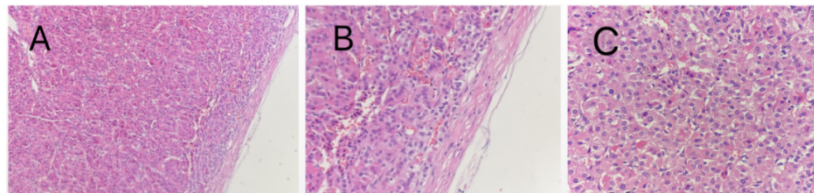
RE: Thank you so much for the heads up, I have made changes to all the issues you mentioned.

1)



(page28 line589)

2)



(page29 line614)

4. Table

- 1) Please add the explanation of * in Table 1 to its footnote. In addition, please add a header to its first column.
- 2) Please add a header to the first column in Table 3.
- 3) If available, please provide more detailed table titles for Tables 1 and 3 to distinguish them.
- 4) Please add a unit to column 3 in Table 5.

490 **Table 5.** To summarize the characteristics of 18 patients with thyroid dysfunction complicated
 491 with RM

Number	Gender	Age	TSH	FT3	FT4	TPOAb	TGAb	K	myalgia	myasthenia	Brown urine
1	M	36	0.01mlu/ml	2.24nmol/L	34.2pmol/L	34IU/mL	<15IU/mL	2.59	Y	Y	N
1(39)	M	49	49.60m	1.79pmol	0.08pmol/	331.90U/	2503.0U/	-	Y	Y	N

RE: Thank you very much for your careful reminders, I have followed the examples you provided to correct the problems with the tables in our manuscript.

1)I'm very sorry for the inconvenience due to my mistake, *in Table 1 means multiply in math.

(page18 line406)

2)We have added a heading in the first column in Table 3 that is Time.

(page23 line476)

3)We have added more detailed table headings for tables 1 and 3.

Tables1.General laboratory tests.

(page18line406)

Tables3 Endocrine-related function tests.

(page23 line476)

4)We add a unit Y/O in column 3 of table 5 (page26 line528)

5. For references cited in **Tables 4 and 5**, please number them according to the first identification of the table in the text. **In your manuscript, Table 4 is cited behind Ref 7. Thus, all references that first appear in Table 4 should be numbered from No.8.** Please check and rearrange all your citations.

RE: Thanks for the suggestion we checked and rearranged all the references.

6. Please check the content whether it should be “17 mm × 11 mm”.

- CT scan of the patient's adrenal gland revealed a round, low-density shadow with a clear edge and a size of about 17 × 11 mm in the right adrenal gland, indicating a right adrenal adenoma (Figure 2). On enhanced scan, a round, low-density shadow with a clear edge and a size of about 17 × 11 mm was observed on the right adrenal gland;

RE:Thank you for the careful reminder, we've already changed it in the manuscript.

(page8 line155-156)