ICMJE DISCLOSURE FORM

Date: Jul. 25th, 2021
Your Name: Yuanyuan Xiao
Manuscript Title: Novel ceruloplasmin gene mutation causing aceruloplasminemia with diabetes in a Chinese woman: a case report
Manuscript number (if known): APM-21-1086-CL

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	Shanghai Municipal Commission of Health and Family Planning Fund Project(20184Y0311)	This payment was made to me.
		Shanghai Sixth People's Hospital East Outstanding Young Fund Project(2019006)	This payment was made to me.
Time frame: past 36 months			
2	Grants or contracts from any entity(if not indicated in item #1 above).	__X__None	
3	Royalties or licenses	__X__None	
4	Consulting fees	__X__None	
5	Payment or honoraria for lectures, presentations,	__X__None	

	speakers bureaus, manuscript writing or educational events		
6	Payment for expert testimony	__X__None	
7	Support for attending meetings and/or travel	__X__None	
8	Patents planned, issued or pending	__X__None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	__X__None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	__X__None	
11	Stock or stock options	__X__None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	__X_None	
13	Other financial or non-financial interests	__X__None	

Please summarize the above conflict of interest in the following box:

This work was funded by grants from the Shanghai Municipal Commission of Health and Family Planning Fund Project (20184Y0311 to Yuanyuan Xiao) and Shanghai Sixth People's Hospital East Outstanding Young Fund Project(2019006 to Yuanyuan Xiao).

Please place an "X" next to the following statement to indicate your agreement:

__X_I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: Jul. 25th, 2021
Your Name: Chaoyu Zhu
Manuscript Title: Novel ceruloplasmin gene mutation causing aceruloplasminemia with diabetes in a Chinese woman: a case report
Manuscript number (if known): APM-21-1086-CL

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ICMJE DISCLOSURE FORM

Date: Jul. 25th, 2021
Your Name: Fusong Jiang
Manuscript Title: Novel ceruloplasmin gene mutation causing aceruloplasminemia with diabetes in a Chinese woman: a case report
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Date: Jul. 25th, 2021
Your Name: Qingge Gao
Manuscript Title: Novel ceruloplasmin gene mutation causing aceruloplasminemia with diabetes in a Chinese woman: a case report
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ID: APM-21-1086-CL
Title:Novel ceruloplasmin gene mutation causing aceruloplasminemia with diabetes in a Chinese woman: a case report

Reviewer A

Comment 1: Could the authors specify what they mean with movement disorder? E.g. parkinsonism, hyperkinetic movements?
Reply 1: we added "involving movement disorder(e.g. motor delay, dystonia, spasticity and parkinsonism)" in the article(see Page 3, line 50-51)
Changes in the text: Page 3, line 50-51

Comment 2: Please add anemia.
Reply 2: we added "anemia" in Page 3, line 49
Changes in the text: Page 3, line 49

Comment 3: What do the authors mean with difficult to identify? As hyperglycemia on its own is not difficult to identify
Reply 3: we added " a diabetes patient combined suffer from ACP" in the last of the sentence. (see Page 3, line58-59)
Changes in the text: Page 3, line 58-59

Comment 4: Were cognitive screening tests performed given?
Reply 4: Sorry, we did not give her any cognitive screening tests.

Comment 5: I doubt whether the cerebral CT findings are indeed indicative of iron accumulation in the brain, given iron is assumed to be iso intens on CT. Was brain MRI performed?
Reply 5: Yes, we agree with the opinion, but it is regretted that we did not performed the cerebral MRI when she was hospitalized in our hospital.

Comment 6: Please remove reticuloendothelial cells, as visceral iron overload in aceruloplasminemia predominantly affects parenchymal cells
Reply 6: Yes, we have removed "reticuloendothelial cells" as advised (see Page 7, line 149).
Changes in the text: Page 7, line 149

Comment 7: As stated above, in my opinion, it cannot be concluded that iron is accumulated in the brain of this patient based on the presented CT images. MRI should be performed to confirm this suscipion.
Secondly, this case it not that different from other ACP patients based on the fact that there were no obvious neurological abnormalities, given the average age of onset of neurological manifestations is around 50 years. Please adjust.
Reply 7: Thank you for the advice. We have made some modification in the text based on the comment. (see Page 8, line 155-159)

Changes in the text: Page 8, line 155-159

Reviewer B

Comment 1:The case report describes blood tests and clinical presentation at diagnosis, with no follow up. The patients is treated with chelating agent, but no information about side effects, how long she has been on the treatment at the time of writing the case report. The case would benefit from a graphical presentation of ferritin concentration over time- before and after the treatment initiation. How did ferritin respond to the therapy?

Reply 1: Thank you for this advice. We have made some modification in the text based on the comment. (see Page 5, line 103-112).

Comment 2: Have the authors considered treatment with free frozen plasma to supplement insufficient ceruloplasmin? Please refer in the discussion to long term follow up in adult patients, how they should be monitored respective of treatment option. Please refer to Tridimas et al JIMD Reports 2020 and many other articles describing treatment options in ACP.

Reply 2: Yes, we also recognized the combination of iron chelation with ceruloplasmin replacement is an effective method to treat the ACP. However, the cost of this therapy is too expensive to afford for this patient because of the low income. Furthermore, there was no formal guidelines for the treatment in ACP, so we did not apply this technology.

Comment 3: The comment regarding ceruloplasmin concentration is missing- was it deficient or insufficient. We know it was low at <0.0183g/L, but it was not deficient. It is likely to be insufficient as she presented later in life with milder symptoms

Reply 3: Thank you for this advive. As mentioned in our report, the homozygous mutations of ceruloplasmin (c.146+1G>A) in this case resulted in a complete lack of ceruloplasmin, and the concentration of serum ceruloplasmin is lower than our limit detection, so it is insufficient. we have modified our text as advised (see Page 7, line 149)".

Changes in the text: Page 7, line 149

Comment 4: Table 1 states all relevant biochemical tests, but no ceruloplasmin or serum copper.

Reply 4: The concentration of serum ceruloplasmin and serum cooper were added into Table 2.

Changes in the text: Table 2

Comment 5: In terms of clinical manifestation, some patients develop leukonychia as a result of long standing iron deficiency anaemia. Was is obvious in this case?

Reply5: No. During the 6 months of follow-up, there was no special abnormalities in her blood routine examination except mild anemia.

Comment 6: Any behavioral problems? Psychiatry problems as a result of iron deposition in the brain?
Reply6: The absence of ceruloplasmin leads to pathological iron overload in the central nervous system. Subjects with ceruloplasmin insufficient would suffered from some neurological abnormalities including neurological symptoms such as blepharospasm, orolingual, mandibular dystonia, chorea, dysarthria, ataxia, parkinsonism, and cognitive decline clinically. Given the average age of onset of neurological manifestations of ACP is around 50 years, the present case also had no obvious neurodegenerative characteristic clinical symptoms and signs expect for presenting mild memory decrease and blunt responses.

Commend 7: What was her education?
Reply 7: Her education was Middle School.

Commend 8: Any plans to perform 24hr urine collection of iron?
Reply 8: Because of the limits of detection capability, we did not detect the 24hr urine iron levels.

Commend 9: She has an effected son. How was she managed during the pregnancy? Has anybody monitored her iron levels, ferritin, LFts, FBC during the pregnancy? Any abnormalities on USS of her liver (during the fetal USS)?
Reply 9: This is the first time we found the pathogenesis of her disease and she did not detect the relative indexes of iron metabolism before. So we had no information about the situation during her pregnancy including the fetal Ultrasound Scanning.

Commend 10: Please correct the spelling ‘awarenesswastakento’ and ‘marriages(4)beforefirstlybeendescribed’ and several other similar typographical errors in the Introduction.
Reply 10: We have modified our text as advised (see Page2-3, line 42-63)

Commend 11: The sentence needs to be rewritten: ‘So far, less than 60 families cases of ACP have been reported world-wide, there was only two cases of ACP has been reported in China before.”
Reply 11:Thank you for the advice. We have modified our text as advised (see Page 6, line 117-120).

Editorial Comments (Please DO NOT delete this section. Editorial comments should also be replied point by point)

1. Please follow the attached "Submission Checklist for Authors" and revise your paper if needed. Here are some additional points:

a. The article already followed a Checklist for reporting standards. Please place "Y" in the "Submission Checklist".

Reply：We have place "Y" in the "Submission Checklist".

b. "Data Sharing Statement" is not required for this paper.
Reply: We have place "N/A" in the "Data Sharing Statement".

c. Conflict of Interest (COI) Form must be provided, as suggested by ICMJE: (http://www.icmje.org/conflicts-of-interest/). Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. COI form download link: https://cdn.amegroups.cn/static/public/coi_disclosure.docx.

Please collect all forms from each author, number all forms in the line-up of authorship and submit them to the editorial office. We also attached two templates for your reference.
Reply: We provided the COI from each author as suggested.

d. Please indicate if any of the authors serves as a current Editorial Team member (such as Editors-in-Chief, Editorial Board Member, Section Editor) for this journal.
Reply: None of the authors serves as a current Editorial Team member for this journal.

e. Please confirm that all figures/tables/videos in this manuscript are original; if not, permission is needed from the copyright holder for the reproduction.
Reply: We confirmed that all figures and tables in this manuscript are original.

f. We are using the "Submission Checklist for Authors" to double-check your manuscript, place "Y" on blank space if you confirm your manuscript has followed the requirement. Place "N/A" if not applicable. If further explanation is needed on a certain item, you can copy the Item and write explanations down below. A filled "Submission Checklist for Authors" should be submitted to the editorial office, along with other required documents.

Reply：We submitted the file "Submission Checklist for Authors" as required.

2. Language Editing

The wordings of the main text and/or figures/tables should be checked by a native English-speaking expert who is majoring in your field. The use of medical writing service (eg., AME Editing Service, http://editing.amegroups.cn/#editing) or an assisting language checker should be acknowledged. We do not publish any ghost-written manuscripts.

***Please resubmit a language-edited version of your manuscript to the editorial office, along with other files (e.g., certificate of language editing).**

***If the language of your paper is polished by a native speaker, please acknowledge his/her assistance in the "Acknowledgement" section. E.g., we would like to thank XXX for his/her help in polishing our paper.**

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Date: Jul. 25th, 2021
Your Name: Huijuan Lu
Manuscript Title: Novel ceruloplasmin gene mutation causing aceruloplasminemia with diabetes in a Chinese woman: a case report
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ICMJE DISCLOSURE FORM

Date: Jul. 25th, 2021
Your Name: Chen Wang
Manuscript Title: Novel ceruloplasmin gene mutation causing aceruloplasminemia with diabetes in a Chinese woman: a case report
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Date: Jul. 25th, 2021
Your Name: Li Wei
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