

Peer Review File

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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 is 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 patient 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 $<0.0183\text{g/L}$, 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 advice. 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 copper 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 it obvious in this case?

Reply 5: No. During the 6 months of follow-up, there were 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?

Reply 6: The absence of ceruloplasmin leads to pathological iron overload in the central nervous system. Subjects with ceruloplasmin insufficiency would suffer 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 except for presenting mild memory decrease and blunt responses.

Comment 7: What was her education?

Reply 7: Her education was Middle School.

Comment 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.

Comment 9: She has an affected 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.

Comment 10: Please correct the spelling 'awareness wastakento' and 'marriages (4) before firstly be described' and several other similar typographical errors in the Introduction.

Reply 10: We have modified our text as advised (see Page 2-3, line 42-63)

Comment 11: The sentence needs to be rewritten: 'So far, less than 60 families cases of ACP have been reported world-wide, there were 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).