Author's response to reviews

Title: Structural and cognitive deficits in chronic carbon monoxide intoxication: a voxel-based morphometry study

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To BMC Neurology
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Dear Professor Ralph Benedict,

Please find enclosed our revised manuscript entitled, “Structural and cognitive deficits in chronic carbon monoxide intoxication: a voxel-based morphometry study” (MS: 1906842155811333), which has been modified in response to your comments. We have thoroughly re-edited the manuscript and the changes are described in detail below. We thank you very much for your consideration.

Yours sincerely and on behalf of all authors,

Hsiu-Ling Chen, MD

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Reviewer (Ralph Benedict):

Thank you for submitting your revised manuscript. It is much improved. However, I find that it is still too lengthy and speculative considering the risk of type 1 error and the small sample size. Therefore, I ask that you attend to the following in what will hopefully be a final revision.

In the RESULTS, do not report on non-significant findings as you do on the top of page 16.

Response:
Thank you for your valuable comments. We have deleted the sentences from the Results section.

In the DISCUSSION, you write that your NP results are consistent with previous studies but you did not include a memory test. This is a major limitation and should be discussed as such.

Response:
Thank you for your comment. We have made revisions accordingly.

1. However, the memory function has not been assessed in this study that may be seen as a limitation. (Line 10 of Page 18)

In the DISCUSSION, on page 19, you recommend clinical treatment which should be retracted or qualified because there are no indicated treatments for this condition.

Response:
Thank you for your comment. We have made revisions accordingly.

1. Long-term follow-up for this particular group is required. (Line 16 of Page 18)

In the DISCUSSION, please remove the following which does not add substantially and is distracting. “Furthermore, extensive hypoxia was found in GM, which was also demonstrated by the SPECT study [11]. The lower perfusion pattern of GM was associated with an increase in disease severity. Our VBM result further supports the idea that DE in CO intoxication, involving both GM and WM, is considered a global distributing disease [11].”

Response:
Thank you for your comment. We have deleted the sentences from the Discussion section.

In the DISCUSSION, please remove the paragraph beginning with “This study shows brain damage to be irreversible ….. provide the psychiatric evidence to clearly support the notion.” It is poorly written, too speculative, and Picture Completion is not a test that is specific to visual perceptive function.

Response: Thank you for your comment. We have deleted the paragraph from the Discussion section.

In the DISCUSSION, the following paragraph should be removed “With the relatively small sample size enrolled in this study, comparison ……. also echoed the VBM results.” Instead, only mention in the limitations paragraph that your sample size is too small for definitive conclusions of DE vs non-DE.

Response: Thank you for your comment. We have deleted the paragraph from the Discussion section and have made revisions accordingly.

1. Our sample size is too small for definite conclusion of DE and non-DE. (Line 7 of Page 21)

In the DISCUSSION, remove all conclusions pertaining to irreversible brain damage, as this is a cross-sectional study.

Response: Thank you for your comment. We have made revisions accordingly.

Finally, the writing remains sub-standard, especially in the ABSTRACT, INTRODUCTION and DISCUSSION. In the Abstract you refer to the left frontal lobes when of course there is only one left frontal lobe. In the Introduction you refer to GM circulation, and you really mean perfusion of blood/oxygen within GM regions. Also, please check spelling (eg amygdala). NP tests are proper nouns and should be capitalized and referenced. Make sure that abbreviations are used correctly, for example, neuropsychological is sometimes abbreviated and sometimes not.

Response:
Thank you for your comment. We have made revisions accordingly.

Left frontal lobes ➔ left frontal lobe
Amygdala ➔ amygdala
Use the abbreviation “NP” to replace the “neuropsychological” thoroughly.

Rather than continue a back and forth on drafts, I have decided to help with the writing and in addition to the above I kindly ask that you simply agree to the following changes, highlighted in gray:

ABSTRACT EDITORIAL CHANGES:

Patients with carbon monoxide (CO) intoxication may develop ongoing neurological and psychiatric symptoms that ebb and flow, a condition often called delayed encephalopathy (DE). The association between morphologic changes in the brain and neuropsychological deficits in DE is poorly understood.

Magnetic resonance imaging and neuropsychological tests were conducted on 11 CO patients with DE, 11 patients without DE, and 15 age-, sex-, and education-matched healthy subjects. Differences in gray matter volume (GMV) between the subgroups were assessed and further correlated with diminished cognitive functioning.

As a group, the patients had lower regional GMV compared to controls in the following regions: basal ganglia, left claustrum, right amygdala, left hippocampus, parietal lobes, and left frontal lobe. The reduced GMV in the bilateral basal ganglia, left post-central gyrus, and left hippocampus correlated with decreased perceptual organization and processing speed function. Those CO patients characterized by DE patients had a lower GMV in the left anterior cingulate and right amygdala, as well as lower levels of cognitive function, than the non-DE patients.

INTRODUCTION EDITORIAL CHANGES:

An increased duration of CO exposure, elevated carboxyhemoglobin (COHb), and damage to the globus pallidus or WM are risk factors for DE [5-7]. DE was associated with WM injury in one study [8], but more research is needed and the long-term prognosis of DE is uncertain. In particular, bilateral, symmetric, confluent areas of signal change in the periventricular WM and centrum semiovale is observed, as
well as cytotoxic edema in studies emphasizing diffusion weighted imaging [9]. A
diffusion tensor study revealed evidence of WM demyelination in DE and bridged
its correlation with cognitive impairment [10].

Other research has emphasized cerebral perfusion in acute CO intoxication
as appreciated with single photon emission computed tomography [11]. The
alteration of cerebral perfusion in the development of DE is unknown. There is
greater consensus that brain atrophy is found in chronic CO intoxication patients
[12-14] as a result of either WM or GM damage. However, little is known about the
association of regional GM atrophy on long-term cognitive outcomes, and the
differences between DE and non-DE groups in this regard.

DISCUSSION EDITORIAL CHANGES:

In the non-DE group, only one significant cluster of lower GMV than controls was
observed, its location in the left post-central gyrus. In contrast, structural
abnormalities in the DE group included lower volume of the left claustrum, right
amygdala, right caudate body, left hippocampus, right inferior parietal lobule, left
superior frontal gyrus, left medial frontal gyrus, right anterior cingulate, left
post-central gyrus, and left mammillary body.

Response:
Thank you for your merciful assistance. We agree to the following changes and have
made revisions in the manuscript accordingly.