Author’s response to reviews

Title: Nitrous oxide induced subacute combined degeneration with longitudinally extensive myelopathy with inverted V-sign on spinal MRI: a case report and literature review

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Response to reviewers

Dear Editors,

Thank you very much for the comments from the editors and two reviewers of our work (NURL-D-17-00241). According to the comments and requests, we have made extensive improvement on our original manuscript, especially according to the requirement of "Case Report". All corrections and supplementary materials are labeled in yellow in our revised version of manuscript. Our detailed point-by-point responses to the concerns are as follows.

We have revised the manuscript in line with all the reviewers’ comments and we hope that the new manuscript can be acceptable for publication at BMC Neurology. If you have any questions, please feel free to contact us.

Many thanks for your processing on our work.

Best regards,

Wenli Hu
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Amir Garakani (Reviewer 1)

This is an interesting and important case study that is relevant to the scientific literature. The authors are able to report a clinical finding that is also supported by neuroimaging results. It is also noteworthy that the patient's vitamin B12 and homocysteine levels were normal, which is unusual but has been reported in other cases of nitrous oxide abuse.

[Reply] Many thanks for this positive comments.

My major criticism is that the authors did not report that there are in fact multiple other case studies reporting subacute combined degeneration in a person abusing nitrous oxide.

BACKGROUND

Lines 5-7: "Only a few case studies..."

Perhaps the authors should re-word this sentence. Please see the review of the case literature (Garakani et al. Neurologic, psychiatric, and other medical manifestations of nitrous oxide abuse: A systematic review of the case literature. Am J Addict. 2016 Aug;25(5):358-69.)

Lines 11-15: "To our best knowledge..."

Again, if you review the above review paper, you will see that there were there were 17 cases of subacute combined degeneration reported.

DISCUSSION

Lines 48-52: "To the best of our knowledge": please check to see if this is accurate (see Garakani review referenced above)

[Reply] Many thanks for this criticism and comment. All the above comments were related to the same question. Literatures were reviewed again through the databases of PubMed, Embase, Cochrane Library and Science Direct. In spite that we have reviewed and cited the above reference, we have got much more information about the SCD induced by N2O. As a result, we have made some improvement as follows (Page 3, Paragraph 1).
Nitrous oxide (N2O), a long-standing anesthetic, is also neurotoxic by interfering with vitamin B12 bioavailability if abused. A few case studies have reported the neurological and psychiatrical complications, even death related to N2O abuse [1]. Among these complications, N2O-induced myelopathy has been regarded as the most common manifestation [1]. To the best of our knowledge, there are only 18 cases describing N2O-induced subacute combined degeneration (SCD), however, to date, only very rare cases with longitudinally extensive myelopathy with inverted V-sign or "rabbit ears" sign on spinal posterior column. We herein described is a 20-year-old female who developed SCD with inverted V-sign on spinal column related to the abuse of N2O.

CASE PRESENTATION

Page 3, Lines 23-24: Please revise as follows: "She had inhaled about 100-200 whipped cream chargers of nitrous oxide (N2O) at a time, for recreational purposes, for at least one year."

Please, also, if possible, clarify what you mean by "at a time". Was this every day?

[Reply] Many thanks for this comment. The patient inhaled the N2O many times daily (not only once). The We have made some improvement as required to be more precise.

Page 3, Lines 27-29: Please capitalize "Mental State". Also please clarify what this score means for the readers who are not familiar with it. Please note that it is out of 30.

[Reply] Many thanks for this suggestion. We have added this information as follows (Page 3, Line 17-18).

The deficit domains of the MMSE included orientation (minus 3 scores), attention and calculation (minus 4 scores).

Page 3, Line 40: Although the authors note that vitamin B12 and homocysteine were normal, please give the actual #'s and reference ranges.

[Reply] Many thanks for this suggestion. We have done as required.
Page 4, Line 5: What was the dose and means of administration of the vitamin B12 (cyanocobalamin)?

[Reply] Many thanks for this suggestion. We have done as required.

DISCUSSION

Lines 58-61: "...developing countries, especially in China": this is redundant from the previous sentence. Please revise. Also, is China a developing country?

[Reply] Many thanks for this suggestion. To date, in spite of developing rapidly, China has been still a developing country, because per capita Gross Domestic Product (GDP) is still lower, ranking 74 worldwide.

Falk Mancke (Reviewer 2)

Did the authors measure methylmalonic acid, antibodies against parietal cells, intrinsic factor and conduct a esophagogastroendoscopy to substantiate their diagnosis?

[Reply] Many thanks for this suggestion and comments. Unluckily, due to technical limits of clinical laboratory in our hospital, we did not test the levels of methylmalonic acid, antibodies against parietal cells and intrinsic factor. As for esophagogastroscopy, it is quite a pity that the patient rejected our request for further investigation.

- Did the authors exclude other sources for the cognitive decline, e.g. did they conduct a thorough neuropsychological/psychiatric examination or did they conduct a cranial MRI.

[Reply] Many thanks for this kind suggestion and comments. In our study, the patient underwent thorough neuropsychological/psychiatric examination in details, and we have excluded other causes of cognitive impairment following results of CSF and serum. The cranial MRI yielded normal findings. We have added this in our revised manuscript (Page 4, Line 3).

The authors should report the deficit areas of the MMSE.
[Reply] Many thanks for this kind suggestion and comments. This was lists as follows (Page 3, Line 17-18).

The deficit domains of the MMSE included orientation (minus 3 scores), attention and calculation (minus 4 scores).

- The authors should add the MRIs from the follow up to show the amelioration of the hyperintensities

[Reply] Many thanks for this suggestion and comments. We have added two figures (Figure 3 and 4) from follow up in our revised manuscript.

- The quality of the figures is inadequate, e.g. in the sagittal plane the alterations are hardly visible: a higher resolution and a smaller field of view are required and the height of the axial planes should be marked.

[Reply] Many thanks for this suggestion and comments. We have done and made some improvement on two original Figures as required (Figure 1 and 2).

- Finally, N20 toxicity has been extensively reported and not only by a "few cases" as stated in the manuscript.

[Reply] Many thanks for this suggestion and comments. This comment was in line with #Review1 and Comment 1. We have made some improvement as required (Page 3, Paragraph 1).

The uniqueness of this case remains limited, the authors need to work this better out. For instance, by better explaining a connection between N20 and the cognitive decline.

[Reply] Many thanks for this suggestion and comments. In the discussion section, we have explored some underlying mechanism of cognitive impairment (Page 5, Line 8-10).