Reviewer’s report

Title: Acute Fatal Posthypoxic Leukoencephalopathy Following Benzodiazepine Overdose - A Case Report and Review of the Literature

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Reviewer: Richard Salazar

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Manuscript Title: Acute fatal posthypoxic leukoencephalopathy following benzodiazepine overdose: a case report and review of the literature

Reviewer: Richard Salazar, M.D.

Comments

Overall this case report presents a very interesting and rare clinical syndrome. The most striking feature of this case report is the acute development of hypoxic leukoencephalopathy which to my knowledge, has never been described in the literature before. Previous reported cases of acute leukoencephalopathy were due to toxins (i.e. chasing-the-dragon toxicity or chemotherapy agents) rather than acute hypoxia. I encourage the authors to further stress out the acute nature of the leukoencephalopathy following acute hypoxia. Below I listed other inquiries and revisions which should be addressed appropriately.

1. Major Compulsory Revisions:

a. Lines 87-91: The psychiatry history could be summarized in the medical history paragraph without the need to further elaborate in too much details.

b. Lines 92-101: Is the antecedent of the previous viral process intended to be linked to the acute hypoxic event and/or leukoencephalopathy? If so, please explain how. Otherwise this paragraph could be omitted.

c. Line 128: Figure 1A rather than figure 1.

d. Line 144: Elaborate further on the description of the mental status and neurologic examination, i.e. following commands, tracking in all directions, spontaneous movements.

e. Line 157: Are the echocardiogram findings relevant to the case? If so, please explain how. Otherwise this findings could be may be summarized as abnormal for “systolic dysfunction”.

f. Line 170: It should read Figure 1B.

g. Line 194: I don’t think you could say that “retrospectively you could see early signs of white matter changes on the first CT head study” if you are reporting the
CT scan as normal under the Case Report section and also in the Figure 1 caption. Unless you intend to change the caption of the Figure 1A to read that “there were early signs of white matter changes”. I personally don’t believe that you could easily see white matter disease in the first CT head.

h. Line 198: The references listed for “opioid overdose” are limited to the intravenous use of heroin leading to acute hypoxia. Our readers could mistakenly believe that this syndrome has been reported only with the recreational use of opioids; however it has been reported after overdose of prescribed oral opioids (Salazar R. Journal of Clinical Neuroscience 2012) or a similar reference.

i. Line 213: This paragraph makes reference to acute toxic leukoencephalopathy, specifically chasing-the-dragon toxicity, rather than posthypoxic leukoencephalopathy. To my knowledge, there is no reports of acute “delayed” posthypoxic leukoencephalopathy. Please include reference to this “acute” subtype of hypoxic leukoencephalopathy if any. Otherwise you should revise this paragraph.

j. Line 279: Elaborate further on the proposed pathophysiology for delayed posthypoxic leukoencephalopathy. Even if it is not fully understood. But more importantly, propose your own hypothesis of why the presentation of your case was so fulminant and acute rather than delayed.

k. Line 285: The outcome is not invariably favorable. For instance, delayed posthypoxic leukoencephalopathy due to heroin may have a poor outcome [Rizzuto et al. Acta Neuropathol 1997]

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests.