Author’s response to reviews

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

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To: Executive Editor of BMC Neurology Journal

Re: Response to the reviewers of our submitted case report titled: Acute Fatal Posthypoxic Leukoencephalopathy Following Benzodiazepine Overdose - A Case Report and Review of the Literature

Dear Dr. T Shipley

I would like inform you that we resubmitted our case report and here is our response to the reviewers’ reports by order:

Reviewer (1):

The authors describe a patient who overdosed on benzodiazepines and cannabis, presented with hypoxic respiratory failure, had a seizures and was essentially brain dead at day 5. They propose that the case was novel because it represent a form of toxic or delayed post-hypoxic leukoencephalopathy (DPHL). They make a case for neither. This appears to be a straightforward case of hypoxic-anoxic brain injury (HAI). DPHL patients do not have leukoencephalopathy at the onset and recover after the first insult. In the case described, there was no lucid interval or delayed demyelination, so this is not a case of DPHL.

We would like to thank reviewer (1) for the time and effort done. However our case we try to report is not a form of anoxic brain injury (ABI) because:

1) Radiological appearance of white matter changes sparing the cortical and subcortical grey matters is against ABI.

2) We believe our case is novel because it represents an acute form of toxic leukoencephalopathy induced by alprazolam. We do not present our case as DPHL; however the MRI (brain) changes are consistent with what had been reported in DPHL.
Plus the fact that reviewers (2&3) accepted this report and neither took it as a straightforward case of ABI.

Reviewer (2):
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.

We would like to thank reviewer (2) for the time and effort done. We considered his suggestions seriously in our updated version of manuscript as follows:
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.
   # We omitted the paragraph (lines 87-91) and included the following statement in the medical history paragraph; “Apart from being easily irritable, more isolated and having sleep difficulties, the patient did not have any major psychiatric disorder. He was a smoker and might have used illicit drugs”.

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.
   # At this point, there is no reason to suspect that is related to illness. So, the whole paragraph was omitted.

c. Line 128: Figure 1A rather than figure 1.
   # “Figure 1” was changed to “figure 1A”

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.
   # The original statement
   “His level of consciousness slightly improved as he starts to open his eyes spontaneously and extends his arms to painful stimulus. There was no verbal response”

Has been as changed to
“His level of consciousness slightly improved as he starts to open his eyes spontaneously, blinked to visual threat, extended his arms to painful stimulus but
was not following commands and there was no verbal output”.

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”.

# We believe the findings on echo are consequent of global hypoxia and hypoperfusion and unlikely to be related directly to the white matter damage. But given the rarity of this entity, the findings were included for future reference.

Nevertheless, we changed the following statement:

“Transthoracic echocardiography was done which showed an evidence of moderate to severe left ventricular dysfunction (an ejection fraction of 35%) with moderate to severe global hypokinesis. His right ventricle was dilated and ejection fraction was also reduced. He has mild to moderate tricuspid and mitral regurgitation with no evidence of vegetations”.

to:

“Transthoracic echocardiography was done which showed an evidence of biventricular moderate to severe global systolic dysfunction”.

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

# We changed “figure 1” was changed to “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.

# This statement was omitted; “Although the MRI was done in the 5th day after hypoxia, the finding of diffuse symmetrical supratentorial white matter changes can be noted retrospectively on the initial CT scan done in day one of admission”.

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.

# The statement “Most commonly, hypoxia induced by carbon monoxide poisoning [2] and opioid overdose.” has been changed to “Most commonly, hypoxia induced by carbon monoxide poisoning [2] and opioid overdose, whither it is a recreational intravenous heroin or medically-used opioids for anaesthesia or oral analgesia [5, 9, 10, 13, 14].

# We added the reference that was suggested article in addition to a reference to
Shprecher et al article in 2008 which included cases associated with methadone and fentanyl.

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.

# The acute type, is what is described in few cases, including ours, where the leukoencephalopathy is evident on imaging in the immediate period after the anecdotal event. There is no period of lucidity or return to normal or near-normal baseline. In other words, it cannot be called “delayed”.

# For example, the first case reported by Ginsberg 1976 is a 23-year-old boy who came with coma secondary to overdose of IV heroin. He remained in poor condition without full recovery of consciousness until he died in day 23 and an autopsy was undertaken and showed leukoencephalopathy. That patient had monophasic course without lucid interval. Although this patient had toxic leukoencephalopathy, it’s definitely not delayed and it was rather acute.

# Also in case number 3 in Bartlett’s (BJR 2005) describes a 43-year-old man who was found unconscious in deep coma with evidence of cocaine, benzodiazepine and lidocaine in his system. This patient had the leukoencephalopathic changes in the first few days of presentation without period of recovery.

# Another example is patient 2 in Rayan’s report in the J Neurol Neurosurg Psychiatry (2005) of a 36 year-old man who was found unresponsive and GCS of 3/15. The event was highly suspected to be secondary to drug overdose due to past history although not confirmed. He then died one after admission. An MRI during that time showed similar changes.

# So, to prevent confusion with chasing the dragon toxicity, we replaced this paragraph;

“The other less common type is the early or acute type where the patient’s brain imaging shows an evidence of leukoencephalopathy in the first few days after the initial event without notable period of recovery”

With; “The other uncommon type is the early or acute syndrome where the brain imaging shows early evidence of leukoencephalopathy in the first few days after the initial event (acute hypoxic coma caused by overdose) without notable period of recovery or lucid period”.

# We are emphasizing on the fact there must be an overdose event with coma and hypoxia, which is different from chasing the dragon where the symptoms are chronic and gradual without coma or overdose event.

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.

# A paragraph was added answering these questions.

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]

# The following statement was added; “Rarely, patients could have progressive neurological deterioration that eventually lead to death within few weeks from the onset of the delayed phase [9]

Reviewer (3):
We would like to thank reviewer (3) for the time and effort done. Our case is accepted by him without any further suggestions.

In addition to the abovementioned changes, we made the following minor modifications:

a) Line 63: "in" was replaced with "on"

b) Line 77: the statement “At the time of the preparation of this manuscript, we were only aware of two cases of leukoencephalopathy associated with the sole use of benzodiazepines was reported only in two publications” was changed to “At the time of the preparation of this manuscript, we were aware of only two publications describing leukoencephalopathy associated with the sole use of benzodiazepines”.

d) Line 200: the word “described” was changed to “reported”

e) This statement was added to the acknowledgements section; “This research is supported by the College of Medicine’s Research Center, Deanship of Scientific Research at King Saud University”.

Bets regards,

Dr. Fawaz Al-hussain FRCPC, MPH
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