Reviewer's report

Title: Analysis of a child who developed abnormal neuropsychiatric symptoms after administration of oseltamivir: a case report

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Reviewer: Ying-Sheue Chen

Reviewer's report:

As a whole, this case report is thorough and comprehensive and is considered to be of value to enhance knowledge in the field regarding oseltamivir and its associated neuropsychiatric symptoms. Several previous case reports have focused on the occurrence of oseltamivir and its neuropsychiatric symptoms but underlying contributing factors are still elusive. This particular case report is the first one that incorporated objective data including EEG, brain MRI, SPECT, CSF and auto-antibody analysis, drug level determination and simulation, and genetic assessment; this is a very important step toward the understanding of the underlying mechanisms.

Major Compulsory Revisions

1. In the Case Report section, paragraph 1, line 9:
The authors listed other medication usage including “hustacodein, ambroxol, benproperine, azithromycin and clarithromycin.” The authors may consider to state whether these medications have any possibility of causing neuropsychiatric symptoms or not.

2. In the Case Report section, paragraph 1, line 16-17:
a. What does the author mean by “defective memory”? Could the author specify it in detail? For instance, is it as a short-term or long-term memory deficit, or is it a semantic or episodic memory deficit?
b. The author included “insisting that she was pregnant” in the parenthesis following “abnormal behaviors”. It may be advisable to list this symptom separately as “delusion of being pregnant” instead of misplacing it under the category of abnormal “behavior”.

3. In the Case Report section, paragraph 1, line 18:
The patient was treated with benzodiazepine administration. Could the author elaborate on the reasons of using benzodiazepine in this patient? Did the author consider about the usage of antipsychotics in the management of psychiatric symptoms? If antipsychotics were ever considered but not prescribed in the end, what were the main considerations?

4. In the Case Report section, paragraph 1, line 26:
The authors reported the result of SPECT with 123I-iomazenil. When is the
SPECT performed, especially in relation to benzodiazepine usage? Is there any possible influence on the SPECT result that may be attributed to benzodiazepine administration? The author may improve the readers' understanding by clarifying these issues.

5. In the Discussion and Conclusions, 1st paragraph, line 1:
The authors stated that “this is the second case report on psychiatric reactions associated with oseltamivir.” I believe this statement is incorrect. As we know, there are several case reports on oseltamivir-related neuropsychiatric side effects in non-psychiatric and psychiatric patients in the past.


6. In the Discussion and Conclusions, 1st paragraph, line 15:
The authors posited that “brain concentration of oseltamivir and/or Ro 64-0802 is likely to be the key determinant of neuropsychiatric side effects.” The author also listed several possible factors that may cause increased Ro 64-0802 level in the brain, such as the use of azithromycin or reduced efflux transport from the BBB. However, the concentration of both oseltamivir and Ro 64-0802 were both below detectible levels in the CSF analysis of the patient. What is the possible explanation of this discrepancy?

7. In the Discussion and Conclusions, 3rd paragraph, line 5:
The authors may consider further delineating “sialidase-related disorders” and its relationship with neuropsychiatric reaction to oseltamivir in more detail and citing a reference.

8. In the Discussion and Conclusions, last paragraph, line 3:
The authors concluded that “factors that might increase the risk of CNS side effects after administration of oseltamivir include Neu2 mutation, GABAergic dysfunction and increased CSF GluRAbs. Except that Neu2 polymorphism may be related to the variation of inhibition of the enzyme by Ro 64-0802 and may be a separate risk factor of oseltamivir related neuropsychiatric symptoms, the other two factors may be viewed as components of limbic encephalitis as described by the authors in previous paragraph in the discussion. Although definite causal relationship is inherently difficult to be confirmed from a case report, I think that the authors should try to discuss whether oseltamivir is possible to induce limbic encephalitis and its subsequent neuropsychiatric manifestations in this patient.
Minor Essential Revisions
1. In the Abstract, Case presentation, line 7: Were the patient’s delirium symptoms disappeared after “benzothiazepine” or “benzodiazepine”?

Discretionary Revisions
nil

**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.