Author's response to reviews

Title: Japanese Encephalitis Accompanied by Cerebral Venous Sinus Thrombosis: A Case Report

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Author's response to reviews: see over
Response to Critique

RE: MS: 1434254832655153

Title: Epidemic Encephalitis Type B Accompanied by Cerebral Venous Sinus Thrombosis: A Case Report

Dear Editor:

Thank you for forwarding the reviewers’ suggestions that have helped improve this manuscript. As requested, the information related to CVT and viral infections, possible mechanisms underlying CVT in this viral infection have been added and now included in the revision. With these added content and additional information for clarification, we now address reviewers’ comments point by point as follows.

Reviewer #1

1) The authors describe a thrombus in the superior sagittal sinus on MRI, but on MRV they state there is only a thrombus in the transverse and sigmoid sinuses.

Thank you for your correction and we have revised the description as follows (see page 5, paragraph 2).

In addition, sigmoid sinus and transverse sinus filling defect were observed, indicating venous thrombosis. Likewise, MRV scan further demonstrated thrombosis in the bilateral transverse and sigmoid sinuses, confirming the diagnosis of CVST.

2) Page 6, 3rd sentence: the statement that "protecting brain cells" is part of "supportive therapeutic measures" seems rather bizarre to me. This does not belong in a scientific medical journal.

Thank you for the clarification and we have revised the description (see page 6, paragraph 2).

Other symptomatic therapeutic measures (including dehydration, antipsychotic therapy, antiinflammatory, antivirus, and body temperature control), and supportive therapeutic measures were taken simultaneously.

3) Page 7, 2nd paragraph: the authors probably mean that IF CVST is related to infection, ENT infection is the most common cause. However, the majority of CVST cases in the modern ages are NOT associated with infections.

We are sorry for the confusion. We intended to describe ENT infection is the most common cause of Lateral sinus thrombosis (LST), rather than CVST. We have corrected the description as follows (Page 8, 2nd paragraph):
Lateral sinus thrombosis (LST) is usually associated with mastoiditis and otitis media, or infection that spreads to sigmoid sinus through a dehiscence in the overlying bone, or the direct dissemination of the infection through the neighboring eroded bone [1-3].

4) Page 4: change to "36 BREATHS per minute"; Page 5: Spelling error in Babinski (first word of page)

We are sorry for the typo and Thank you for your correction. We have changed to "36 breaths per minute" (see page 4) and “Babinski” (see page 5).

Reviewer #2

1) Background: Add information related to CVT and viral infections. There are many viruses reported to be associated with CVT. Association of CVST with meningitis and encephalitis.

Thank you for the clarification. We have added this issue in the section of background (See page 4, paragraph 1). The added details are as follows:

There are many viral infections documented to be associated with stroke, such as varicella-zoster virus [2, 3]. Furthermore, cerebral venous thrombosis (CVT) was also identified in a patient presenting with fever convulsions, and associated herpes simplex encephalitis [2, 3]. Viral hepatitis is being regarded as a rare infective cause of CVT [2, 3]. JE virus is also a common cause for cerebral ischemia in children [2, 3]. However, JE with CVST has not yet been reported literally.

2) Any test done for hypercoagulable work up?

The antiphospholipid antibodies test was negative. Unfortunately, further assessment of procoagulant state including protein C, protein S, antithrombin III, factor V, were not performed. So, we speculated that combination of systemic infection and dehydration might contribute to the hypercoagulability of this patient.

3) IgM antibody was checked in serum or CSF? Titers?

We recognized the possibility of JE, so we reported to CDC as soon as possible. We investigated his serologic JE-specific IgM antibodies twice, the first was weakly positive, and the duplicated result showed positive one week later. As the patient’s blood was sent to the CDC for detection, the specific titer was not assessed. We performed a Lumbar Puncture as the psychiatric symptoms of our patient were under
control, his serologic JE-specific IgM antibodies were both positive, so we did not further investigate his JE-specific IgM antibodies in CSF. We have added the information for clarification as below (see page 7, 2nd paragraph):

In addition to intracranial hypertension, our patient’s other characteristics can be summarized as follows: 1) A 17 years old man, acute onset of symptoms; 2) High fever (39°C), and confusion; 3) Abnormal reflexes and meningeal irritation positive; 4) Summer season, with a history of mosquito bites; 5) MR imaging of brain showed bilateral thalamic swelling, enhanced scan showed marked leptomeningeal enhancement; 6) White-cell counts and neutrophil counts raised. According to its characteristics, we further investigated his serologic JE-specific IgM antibodies twice, the first was weakly positive, and the second result showed positivity one week later, suggesting that the antibody levels increased.

Due to its complexity, JE virus isolation is not a routine method for laboratory diagnosis. Detecting serologic JE virus antibodies was currently the main laboratory diagnostic method. As the patient was a soldier, we were unable to obtain epidemiological data on admission. Later, one of his comrades (living in different camps in the same county) who appeared to have similar symptoms, was also diagnosed with epidemic encephalitis type B, thus conferring evidence to the location of mosquito borne disease in their case. We further performed a Lumbar Puncture when the psychiatric symptoms of our patient were under control. As his serologic JE-specific IgM antibodies were positive, we did not further investigate his JE-specific IgM antibodies in CSF. This case reminds us that the possibility of JE should be considered if a patient is with high fever, headache, and impaired consciousness in late summer and autumn. For the suspicious cases, the epidemiological data should be repeatedly obtained and investigated as well as reported to CDC immediately.

4) Why repeat MRI showed bilateral thalamic enhancement?
We are sorry for the confusion. The repeat brain MRI scan revealed slight swelling of bilateral thalamus, other than enhancement. We have corrected the description as follows (see Page 6, 2nd paragraph):

The patient was discharged on August 23th, 2010 and transferred to a local hospital for further treatment. The repeat brain MRI scan revealed mild oedema over bilateral thalamus. Compared to the MRI result of August 6th, 2010, the lesion diminished significantly.
5) Discuss possible mechanisms underlying CVT in this viral infection.

We have added the information of this issue in the section of discussion (see page 9, paragraph 1).

In addition, the possible mechanisms underlying CVT in JE viral infection can be summarized as follows: 1) the penetration of virus through the endothelial walls contributed to an increase in the permeability of the cerebral vessels (capillaries and precapillaries)[2, 4, 5]; 2) JE virus could induce increases in the level of interleukin-6 and tumor necrosis factor-α which are risk factors for thrombosis [2, 4, 5].

Moreover, we have checked the English writing of this paper carefully, and have asked a native speaker to edit the paper.

We trust that you find the revision in accord with the reviewers’ comments and the quality of the manuscript improved substantially. Thank you for re-considering our manuscript.

Sincerely yours,
Nian Xiong