Author’s response to reviews

Title: Deep cerebral venous thrombosis mimicking influenza-associated acute necrotizing encephalopathy: a case report

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To Reviewer #1:

# 1. L68: "Diagnosis is delayed by misdiagnosis …" I suggest leaving 'by misdiagnosis', as this is redundant.
Response: As suggested by the Reviewer, we have deleted the phrase “by misdiagnosis”.

# 2. L81: "Her medical and family histories were unremarkable" - as with the use of data, the singular of history sounds more familiar to me - up to the editorial office to decide…
Response: As suggested by the Reviewer, we have changed this to the singular form “history”.

Diagnosis of DCVT is often delayed because its clinical manifestations (headache, altered consciousness, mental troubles and motor deficits) are nonspecific and variable [10].
Her medical and family history was unremarkable.

# 3. L87: please check again on the level of consciousness in the Glasgow Coma Scale scoring: with E=2, hasn't the patient rather been stuporous?

Response: As suggested by the Reviewer, “stuporous” is a more appropriate description. We have revised the sentence, as follows:

On admission, neurological examination revealed that the patient was stuporous, with a Glasgow Coma Scale score of E2V4M6.

# 4. L121: "Because drainage through the basal vein of Rosenthal and the superficial cerebral veins was observed, we did not attempt invasive therapeutic procedures, and continued treatment with intravenous glycerol (400 mg per day) and intravenous heparin, followed by warfarin."

a. The sentence still reads as if you were treating cerebral venous thrombosis (CVT) with osmotic agents. This is only clarified within the discussion, where you refer to the treatment of elevated intracranial pressure (ICP).

b. Currently there is no statement regarding an actual invasive measurement of ICP. Has this been done, and if so, using which device and which access?

c. I'd divide this sentence, specifying the osmotic treatment was given because of disturbed level of consciousness due to PRESUMED elevated intracranial pressure.

Response: The invasive intracranial pressure monitoring was not performed during the course of illness. We have revised the sentence, as follows.
Treatment with intravenous glycerol (400 mg per day) was also continued because we presumed that disturbed level of consciousness was partly due to elevated intracranial pressure, although intracranial pressure monitoring was not performed.

Response: We agree with the Reviewer that it is more appropriate to describe the anticoagulant therapy and osmotic treatment separately. We have revised the description, as follows:

Because drainage through the basal vein of Rosenthal and the superficial cerebral veins was observed, we did not attempt invasive therapeutic procedures, and continued treatment with intravenous heparin, followed by warfarin. Treatment with intravenous glycerol (400 mg per day) was also continued because we presumed that disturbed level of consciousness was partly due to elevated intracranial pressure.

# 5. L180: "Although both DCVT and ANE are associated with normal white-cell counts in CSF, xanthochromia with a high red-cell count, as observed in our patient, may indicate venous infarction resulting from DCVT, because previous cases of ANE have not shown these results [2]."

From my clinical experience, DCVT is not usually associated with CSF xanthochromia (in the rare case patients with sinus thrombosis receive CSF analysis). Please discuss the mechanism you hold responsible for blood metabolites within CSF due to DCVT. This would require diapedesis of erythrocytes into the CSF. So far a potential causal link is not yet overtly presented.

Response: As suggested by the Reviewer, we have revised the description, as follows:

Although both DCVT and ANE are usually associated with normal white-cell counts in CSF, xanthochromia with a high red-cell count, presumably resulting from disruption of the blood-brain barrier due to venous infarction, has been reported in cerebral venous thrombosis [19, 20], but not in previous cases of ANE [2].
# 6. L189: "The current standard methods for making a diagnosis of DCVT are cerebral angiography, MRV and computed tomography angiography. However, these neuroimaging studies are not performed routinely." This is misleading. When cerebral venous thrombosis is suspected, cerebral imaging is strongly indicated. Does the second sentence within the citation above refer to ANE?

Response: We agree with the Reviewer that the original description was misleading. In addition, we agree that “when cerebral venous thrombosis is suspected, cerebral imaging is strongly indicated”. Thus, we deleted the sentence “However, these neuroimaging studies are not performed routinely” from the revised manuscript.

# 7. Conclusion:

"If bilateral thalamic lesions are identified in patients with influenza infections, immediate diagnosis and treatment of ANE is important. Simultaneously, DCVT should also be kept in mind, because delayed initiation of anticoagulant therapy can lead to unfavorable outcomes."

In my opinion, one of the main messages of this case report is the striking similarity of neuroradiological imaging findings of both the extremely rare ANE and the still rare (but from an epidemiological perspective much more frequent) CVT. Thus, I recommend to further stress the importance of cerebral MR-imaging aiming at increasing clinical certitude that the patients with the imaging findings shown in this report are not affected by CVT. With the current phrasing, those readers, who only read the conclusion, will miss this important teaching point.

Response: As suggested by the Reviewer, we have revised the manuscript, as follows:

[L213-216]

If bilateral thalamic lesions are identified in patients with influenza infections, DCVT as well as ANE should be kept in mind, and T2*-weighted imaging could be a useful sequence for discriminating DCVT from ANE.

# 8. Figure 1, line 8: "small hyperintensity areas" should be changed to 'hyperintense areas';

Line 12 and second-last line: "abnormal signals" should be changed to 'signal' (singular)

Response: As suggested by the Reviewer, we revised the manuscript, as follows:
At day 7 after admission, small hyperintense areas were observed in the anterior and left posterior regions of the thalamus in a T1-weighted image.

A T2*-weighted image showed hemorrhagic changes in the thalamus with right-side predominance, but abnormal signal from deep cerebral veins was less prominent than at admission.

Abnormal signal of deep cerebral veins was not present in a T2*-weighted image.