**Author’s response to reviews**

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

**Authors:**

Daisuke Taniguchi (dtanigu@juntendo.ac.jp)  
Sho Nakajima (synakaji@juntendo.ac.jp)  
Arisa Hayashida (arisa-h@juntendo.ac.jp)  
Takuma Kuroki (tkuroki@juntendo.ac.jp)  
Hiroto Eguchi (heguchi@juntendo.ac.jp)  
Yutaka Machida (ymachida@juntendo.ac.jp)  
Nobutaka Hattori (nhattor@juntendo.ac.jp)  
Hideto Miwa (hmiwahmiwa@gmail.com)

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**Author’s response to reviews:**

Dear Dr. Nakahara, Editor,

**Journal of Medical Case Reports**

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

(JMCR-D-16-00816)

Please find attached the revised version of the manuscript by Daisuke Taniguchi et al., which we would like to submit for publication in the Journal of Medical Case Reports. We thank you and the reviewers very much for your careful consideration of our manuscript. As suggested by the reviewers, we have revised the manuscript.

We hope that our revised manuscript is now acceptable for publication in the Journal of Medical Case Reports.
Yours sincerely,

Hideto Miwa, M.D.

Department of Neurology, Juntendo University Nerima Hospital

To the Editor:

#1, In your submission of the revised manuscript, please attach a certificate by an English editing service (or an editor) indicating that the manuscript has been edited for the language.

Response: The English in our manuscript has been edited by an English-editing service, Edanz. Please confirm that a certificate was attached as an additional file.

To Reviewer 1:

(1) Introduction, first paragraph, second sentence: the authors might state the approximate no. of reported patients with ANE in viral infection in case reports and case series.

Response: As suggested by the Reviewer, it is relevant to know the number of reported patients with ANE in viral infection. However, the exact number of the patients remains undetermined. We have added the description, as follows:

[Line 55–56]

To date, publications relating to ANE have been limited to case reports and small case series, and the exact prevalence and incidence of ANE remain undetermined [2–8].

(2) Line 64: Please specify that edema and/or hemorrhage as a complication of deep CVST result in lesions of the thalami.

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

[Line 64–68]
For example, the neuroimaging features of deep cerebral venous thrombosis (DCVT) may sometimes be shared by ANE, because thrombosis of the internal cerebral veins, the basal veins, and the great cerebral vein eventually lead to venous (hemorrhagic) infarction and vasogenic edema of bilateral thalami [4].

(3) Case presentation: please add the group (neuraminidase inhibitor) of Laninamivir and way of administration.

Response: As suggested by the Reviewer, we have added the detailed description of treatment, as follows:

[Line 84–85]
She received treatment with a single oral inhalation of 40 mg laninamivir octanoate hydrate, a neuraminidase inhibitor.

(4) Line 86: Are there numbers about the frequency of positive D-dimer testing in case of influenza infection? Might D-dimer levels help to discriminate CVST from other infectious disease? If so, please add this aspect in the discussion section.

Response: As suggested by the Reviewer, we added the following sentences into ‘Discussion’ section, as follows:

[Line 175–179]
With regard to laboratory findings, an elevation of the level of D-dimer, which is found in most patients with DCVT, might be expected to be a strong clue to diagnosis of DCVT; however, this result is observable nonspecifically in a wide variety of frequently encountered conditions, such as dehydration or prolonged bed rest [10].
(5) Line 92: How can CSF xanthochromia be explained (disturbed blood-brain-barrier? Venous stasis infarction?)?

Response: As suggested by the Reviewer, we have added the following sentences into ‘Discussion’ section, as follows:

[179–183]

Instead, CSF findings may be helpful to differentiate DCVT from ANE. Although both DCVT and ANE are associated with normal white-cell counts in CSF, xanthochromia with 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].

(6) Differential diagnosis: Did the treating physicians despite low CSF neutrophil count screen for other causes of infectious / viral encephalitis (PCR, serology)?

Response: We checked the CSF culture and PCR assay. As suggested by the Reviewer, we added detailed a description of CSF tests and discussion, as follows:

[98–102]

CSF bacterial, fungal, and mycobacterial cultures were performed, with negative results. Polymerase chain reaction assays of CSF for herpes simplex virus, varicella zoster virus, Epstein–Barr virus and cytomegalovirus all had negative results.

[179–183]

Instead, CSF findings may be helpful to differentiate DCVT from ANE. 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].
(7) Line 122: For clarity, please add the reason for HLA-B51 typing. Screening for cancer using tumor markers is usually not recommended. As CT-Screening was negative the additional information on tumor markers should be left.

Response: As suggested by the Reviewer, we deleted the information on tumor markers and screening of collagen diseases. [Line 133-143]

(8) Discussion: Although deep cerebral venous thrombosis (DCVT) and ANE are both relatively rare, DCVT seems to be far more frequent (see first comment regarding introduction). ANE is an exclusion diagnosis and requires - among others - the exclusion of CVST. The current standard of CVST diagnosis is CT- or MR-venography. Implicit, this has not been performed initially. These aspects are not yet discussed and should be added.

Response: As suggested by the Reviewer, we added a detailed description of the diagnostic methods for DCVT, as follows:

[189–194]

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. Meanwhile, recent studies have highlighted the clinical benefit of T2*-weighted imaging of DCVT, in which the thrombosis gives a hypointense signal [19] [20].

(9) Line 114: Please state the rationale for treatment with osmotic agents, substances, dosage and route of administration. Might the dehydratating effects of the osmotic agents explain pulmonary embolism and deep venous thrombosis?

Response: As suggested by the Reviewer, we added a detailed description of the osmotic agents and the reason for using osmotic agent to treat DCVT, as follows:
Guidelines for treatment of DCVT recommend dose-adjusted intravenous administration of heparin, followed by oral anticoagulants [10]. In addition, if intracranial pressure is severely raised, as in our patient, treatment with osmotic agents is recommended [10]. By contrast, treatments for ANE, including intravenous administration of steroids and immunoglobulins, potentially cause hypercoagulability, which might lead to exacerbation of DCVT.

(10) The case report could be further improved by comparing (what do they have in common) and contrasting (how can they be differentiated) ANE and CVST in more detail, in addition to the presented information. I suggest adding one or two brief paragraphs in the discussion section adding a very brief description of histological changes due to ANE vs. CVST, clinical presentation concentrating on the symptoms of this reported patient, diagnostic strategies including imaging findings in both entities (please focus on MRI-sequences), and treatment. In my opinion naming differences of treatment is clinically especially relevant as corticoid treatment has pro-coagulatory effects and thus is not indicated in the treatment of CVST.

Response: As suggested by the Reviewer, we have added the detailed discussion on the differential diagnosis between ANE and DCVT into the ‘Discussion’ section. In addition, we have added a new paragraph which includes discussion about the therapeutic guidelines for DCVT.

Guidelines for treatment of DCVT recommend dose-adjusted intravenous administration of heparin, followed by oral anticoagulants [10]. In addition, if intracranial pressure is severely raised, as in our patient, treatment with osmotic agents is recommended [10]. By contrast, treatments for ANE, including intravenous administration of steroids and immunoglobulins, potentially cause hypercoagulability, which might lead to exacerbation of DCVT.

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. Meanwhile, recent studies have highlighted the clinical benefit of T2*-weighted imaging of DCVT, in which the thrombosis gives a hypointense signal [19] [20]. This finding is detectable in ~90% of sites of DCVT at the first MRI investigation, suggesting that T2*-
weighted imaging is valuable for clot detection in DCVT in conjunction with conventional MRI, especially in the acute phase of thrombosis [20].

(11) Fig 1D: the dilated deep cerebral veins could be emphasized e.g. by a box or arrows. It might be even more illustrative to add a magnification of this finding.

Response: As suggested, the figure has been revised. We have added a magnification of the finding.

(12) Fig 4: Please give the administration route of Peramivir. Typing errors in figure 4 (warfarin, GCS).

Response: As suggested, we have added the description on the administration route of Peramivir, and the figure has been revised.