Author's response to reviews

Title: A successfully treated case of herpes simplex encephalitis complicated by subarachnoid bleeding: a case report

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Michael Kidd, MD
Editor-in-Chief : Journal of Medical Case Reports

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" A successfully treated case of herpes simplex encephalitis complicated by subarachnoid hemorrhage: a case report"

Dear Dr. Kidd,

We are returning herewith the above manuscript revised according to your letter dated on May 7th, 2010.
The Editor’s replacements are very helpful to revise manuscript.

We would be grateful if the manuscript could be considered for publication in your journal, Journal of Medical Case Reports.

Sincerely,

Hiroshi Kataoka, MD.PhD
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Editors
Please restructure the abstract into the following three sections: Introduction, Case Presentation and conclusion
As suggested, we modified the abstract.

Please include the ethnicity of the patient in the case presentation section of the manuscript
As suggested, we added the ethnicity of the patient in the Case presentation.

Reviewer 3
1. There are no clear descriptions of psychopathology, other than ‘delusional thinking’. The first sentence in INTRODUCTION has a spelling error ‘fetal’ that should be ‘fatal’
   According to reviewer’s suggestion, we added the descriptions of psychopathology and modified to the ‘fatal’.

2. The CSF glucose is not mentioned for every LP done
   As suggested, we added the CSF glucose of every LP.

3. The case report has emphasised on the relationship/correlation between CSF real time PCR and CSF HSV-I IgG & IgM which is not necessary. For diagnostics of HSVE, CSF real time PCR HSV-I is conclusive. Is this narrative (PCR versus HSV IgG/IgM) required in the case report?
   As pointed out concerning the relation between CSF PCR and CSF HSV-I IgG & IgM, we agree that CSF PCR is conclusive for the diagnose of HSVE, but the results of PCR in CSF become negative after 5 or more days from the onset of neurologic symptoms [1]. In patients with suspected HSVE, intrathecal antibody synthesis of HSV is useful for the diagnosis of HSVE: for example, a serum/CSF HSV ratio of ≤20 or positive titers of HSV in paired CSF samples. The specificity of the antibody ratio for estimating intrathecal antibody synthesis has been reported to be 91% [2]. Thus, we emphasized the relation between CSF PCR and CSF HSV-I IgG & IgM for the diagnosis or management of HSVE.

References:

4. The recommended course of Acyclovir is for 14-21 days; here the authors gave Acyclovir for only 10 days. Why?
5. On Day 11, Real time PCR HSV-I became negative, suggesting the eradication of HSV-I in CSF; why was antiviral treatment switched to parenteral vidarabine?
   As pointed out concerning the duration of antiviral treatment, since the titers of HSV-1 IgM and IgG antibodies in CSF had increased in parallel to increases in CSF lymphocytes
and red cells, and MRI abnormalities had worsened, we switched from acyclovir to intravenous vidarabine. Moreover, intrathecal HSV genomes cannot be detected more than 5 days from the onset of neurologic symptoms [1], and CSF PCR becomes negative after acyclovir treatment, similar to our patient [3]. Because antiviral treatment lowers the HSV DNA concentration in the CSF it is difficult to determine the sensitivity of PCR when patients are receiving antiviral treatments [3]. Thus, we considered that HSV PCR in CSF in our patient had become negative at that time.

Reference

4. Why was Dexamethasone and intravenous Immunoglobulin added to the regimen?
As for dexamethasone and intravenous immunoglobulins, a multiple logistic regression analysis recently showed that steroid treatment is effective for HSVE [4], and now randomized, double-blind trials of steroids for HSVE are in progress [5]. Intravenous immunoglobulins are well known to be indicated for severe infectious diseases such as encephalitis and were reported to be effective treatment for encephalitis [6]. Thus, we used these treatments.

References:

6. What was the indication of multiple LPs; Day 7, Day 11, Day 39?
We performed these follow-up LPs to evaluate the disease severity or the response to these treatments since the consciousness level was reduced and cranial neuroimaging abnormalities persisted. We added the reason for repeated LPs to the text.

7. It is difficult to logically conclude the aetiology for Day 26 deterioration in consciousness and desaturation; it is most likely due to right pulmonary artery thrombosis (Pulmonary embolism) rather than the CT evidence of subarachnoid haemorrhage with intraventricular extension. The CT evidence of a localised left perisylvian bleed with intraventricular bleed does not seem to have clinical relevance, and represent an incidental finding.
As pointed out the reviewer’s suggestion, we agreed it and modified the case report.

8. Is the aetiology of pulmonary embolism a well recognised thrombotic complication of intravenous immunoglobulin?
As pointed out concerning the aetiology of thrombosis, we believed the aetiology involved a hypercoagulative state rather than intravenous immunoglobulin because the persistently high titer of serum D-dimer, which is well known to be a sign of hypercoagulation in conditions such as deep vein thrombosis [7], and the dose of short-term intravenous immunoglobulins was small as compared with that used in GBS or CIDP. We added the D-dimer to the case report.

Reference:

9. On Day 5 there is CT Brain evidence of hemorrhagic necrotizing process in the left amygdaloid body. The CSF after day 5 onwards shows increasing RBCs. This would suggest RBC diapedesis from the amygdaloid body into the adjacent CSF spaces. Perhaps an earlier CT than Day 26 would have shown subarachnoid bleed with intraventricular extension. This would mean that the subarachnoid bleed is not primary and secondary to the hemorrhagic necrotizing process in the left amygdaloid body.
As suggested, we modified the manuscript.

10. I would certainly hesitate to advocate or recommend that anticoagulation is safe in the treatment of pulmonary thromboembolism with co-morbid intracerebral hematomas and subarachnoid bleeding. Would a viable alternative be percutaneous catheter thrombectomy/rheolytic thrombectomy?
As pointed out concerning IVR therapy, we consulted radiologists but because of technical problems, we could not perform percutaneous catheter thrombectomy/rheolytic thrombectomy.

The subarachnoid bleeding with intraventricular extension does seem to be an extension of the left amygdaloid body hemorrhagic necrotizing process rather than unexpected DE-NOVO subarachnoid bleed complicating HSVE.
As suggested, we modified the manuscript.

Furthermore, previous reports of complicating intracerebral hematoma either early or late in the course of HSVE, occurred in the same areas of abnormal signal intensity on MRI (encephalitic/cerebritis areas) eg report by Jabbour. New areas of hemorrhage have also been reported. Why did anticoagulation in your case spare these "encephalitic areas" as shown in the intial MRI (Fig A/B)?
As pointed out concerning hemorrhage and HSVE lesions, increased abnormal signals were evident in the left amygdaloid body, where hemorrhage occurred later. We have provided an MRI image (Fig A) showing abnormal signals in the amygdaloid body. To avoid confusion, we revised the initial MRI results and figure legend.