Author’s response to reviews

Title: A case report of iatrogenic deterioration of yet undiagnosed Rhombencephalitis; always be careful with corticoids.

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Author’s response to reviews:

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Dear editor

First of all we want to thank the reviewers for reviewing our case report. We appreciate their constructive feedback and we hope we did improve our manuscript with the suggestions they made. Answers to the different questions and description of the corrections we made in the text are listed below.

Sing Sing Way (Reviewer 1):

Background:

Page 2, Lines 23: We removed the phrase "until now" and capitalized and italicized "Listeria monocytogenes."

Case Presentation:

Page 2, Lines 40-41: We adjusted the phrase to "progressive perioral numbness."

Page 2, Line 46: The phrase was changed to "initial diagnosis"

Page 2, Line 46: Was the patient diagnosed with a vertebrobasilar stroke or a TIA? - This is not clear. We agree that this is not clear. After revising the patient chart, the initial differential
diagnosis was a cerebrovascular accident, definitely not a transient ischemic attack. Therefore we changed this in the text of the manuscript.

Page 2, Line 52: "liquor" was changed to "CSF"

Page 2, Line 59: The phrase "because a sudden Borrelia sero-conversion, in combination with a recent history of a tick bite,..." is awkward and unclear. Was the patient tested for Borrelia on admission and then again after being admitted for several days? How many days had the patient been ill by this time? - Indeed, the patient was tested for Borrelia at presentation, the serology IgG and IgM was then negative. After 15 days the test was repeated, because the patient mentioned a recent tick bite and then it was positive for anti- Borrelia IgG antibodies. We added this to the text. So, the patient was ill for 15 days before the serology turned positive. (we don't think this “seroconversion” was relevant, however the treating neurologist thought it was and acted accordingly)

Page 3, Lines 4, 11, and 17: How different were the various states of hemiparesis ("subtle" from "distinct" from "full")? Were there any more objective measurements of strength, reflexes, etc? - After reviewing the patient chart for the level of hemiparesis, we discovered that the hemiparesis was already diagnosed as complete when the patient was transferred, so grading wouldn’t make sense in this case. We are sorry for the confusion.

Page 3, Line 21: The phrase was changed to "A new interview with the family after ICU admission revealed...."

Page 3, Line 22: We changed the word “formation” to "information".

Page 3, Line 26: Why amoxicillin instead of ampicillin for intravenous administration? - In the Netherlands, ampicillin is not available and therefore not used. Amoxicillin is administered following the Dutch guidelines for treatment of Listeria Monocytogenes.

Page 3, Line 29: We italicized the name of the organism Listeria monocytogenes. What day of illness was the culture drawn and what day of illness did the culture become positive? - The blood culture was drawn on day 22 of the illness and two days later (day 24) it became positive. The gram stain of the CSF taken at the ICU showed gram positive rods the same day. To make the case more clear, we added this to the text.

Page 3, Line 34: The phrasing of the sentence suggests that the treatment being offered was inappropriate.- Within this sentence, “dispropriateness” is used as a more appropriate alternative for “futile” [ref: Current Opinion 2013, Erwin J.O. Kompanje, Causes and consequences of disproportionate care in intensive care medicine], to elucidate the meaning we made some adjustments to the sentence and spelling.

Page 3, Line 37: We changed the word "pyogenes" to "pyogenic."
We tried to adjust some of the phrasing to make the story more straightforward. For the chronology of the illness, we added some extra information and we want to refer kindly to the included time scheme in which the chronology is clearly illustrated.

The words ‘even’, ‘immediately’ and ‘extremely’ are removed from the case presentation.

Discussion

Page 3, Line 50: We improved the readability by dividing the sentence in two parts.

Page 3, Line 57: We capitalized and italicized "Listeria."

Page 4, Lines 5-15: This is an important point that I think could be more strongly emphasized in a succinct way. Is there literature on what other hospitals have done (ie, algorithm with addition of fungal or more bacterial coverage after a certain number of days of illness, an interview checklist, etc)? - Unfortunately there is as far as we know no literature available on these subjects. The only literature available is the case reports we used, unfortunately in none of them these issues are covered.

Page 4, Lines 16-26: Description of the epidemiology of listeriosis and rhomboencephalitis is interesting and important. This could probably be incorporated into the first paragraph, however, as some of the information seems redundant and there is a lack of flow between the above paragraph (lines 5-15) and this paragraph. - We have rearranged the text of these paragraphs, to make them fit better together and to keep the flow. Redundancies and repeats were deleted.

Page 4, Line 28: "Substitute" is changed to "adjunctive"

Page 4, Lines 30-34: The paper by Brouwer mentions a decrease in mortality in Streptococcus pneumoniae meningitis as well as decreased hearing loss and neurologic sequelae in some groups but the mortality was not decreased overall for all groups. The authors concluded that corticosteroids may be useful in patients with bacterial meningitis in high-income countries although the data may be interpreted differently by readers. - We agree with your comment, that’s why we added some extra information to avoid misinterpretation.

Page 4, Lines 39-41: How many days did the patient have symptoms without antimicrobial therapy? I am more concerned that delay in appropriate antibiotics was a greater contributing factor than the steroids. The patient of this case description, had symptoms for 22 days before adequate antibiotic treatment was started. - We agree that delay in appropriate treatment has a great contribution in the disastrous course of the illness, but in our opinion the corticosteroid could be “the straw that breaks the camel’s back”. If there had not been such long delay in adequate therapy, the corticosteroid administration would probably have been less disastrous. In
the end, we will never know if the patient would have survived if the corticosteroid therapy had not been given.

Conclusion

Page 4: Line 54: The sentence "Therefore a thorough interview is essential…" is a true statement but awkwardly worded. - We changed this sentence to make it more clear.

Tables and Figures

Picture 1: We spelled out the full word for FLAIR

Picture 3: Please include any stains used and what the images show specifically such as mixed nuclear inflammatory infiltrates. - We added this information to the pictures

Claudia Gravekamp (Reviewer 2): Comments to authors

It seems the correct conclusion, i.e. that corticosteroids may have promoted the growth of Listeriosis. Since the Listeriosis is difficult to diagnose in the early stage (like many other types of sepsis), may be a more sensitive assay could be used. For instance, a PCR specific for Listeria on blood, liquor and urine may provide an earlier diagnosis compared to the blood and liquor culture. This could be mentioned in the discussion. - Thank you for this suggestion, we added the possibility of using a PCR, including a reference, to the discussion section.

We sincerely hope that the manuscript improved significantly after implementation of the feedback of the reviewers. Hopefully the case report now meets your expectations for publication in your valued journal

Yours sincerely,

Loes Mandigers and Jelle Epker