Author's response to reviews

Title: Tick borne encephalitis without cerebrospinal fluid pleocytosis

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Version: 3
Date: 8 September 2014

Author's response to reviews: see over
September 8, 2014

Dr. Danielle Talbot, Assistant Editor
BioMed Central
*BMC Infectious Diseases*

Dear Dr. Talbot,

Please find enclosed a revised version of our manuscript entitled “Tick borne encephalitis without cerebrospinal fluid pleocytosis” by Daša Stupica, Franc Strle, Tatjana Avšič-Županc, Mateja Logar, Blaž Pečavar, and Fajko F Bajrović. We are grateful to the reviewers for their thoughtful critique of our manuscript and made appropriate changes to the text. We believe that these revisions address the concerns raised by the reviewers and result in a stronger manuscript. Our detailed responses to reviewers’ comments are listed below.

Thank you for considering this manuscript for publication in BMC Infectious Diseases.

We hope that our revised manuscript is now acceptable for publication.

Sincerely,
Daša Stupica
Response to reviewer 1

We thank the reviewer for the comments. We appreciate that the reviewer found that our case is noteworthy.

Response to reviewer 2

We thank the reviewer for the thoughtful critique of the manuscript. We try to address the comments in detail below.

Introduction

Comment 1: It is not true that the first description of lack of pleocytosis in encephalitic TBE cases is by Pöschl et al, although, this reference is focused on this fact and well worth mentioning but also then together with other previous publications showing this.

Response: We made appropriate corrections in our manuscript according to the reviewer’s comment. In the revised version of our manuscript we added the two references proposed by the reviewer.

We highlighted the case by Pöschl et al, because they were the first to focus on the lack of pleocytosis in TBE patients and were the first to provide detailed clinical and microbiological description to substantiate this entity. In the three cases described by Cruciat et al, the diagnosis of TBE was not well established. The fact that in an area which was not known to be endemic for TBE such as North-Eastern Italy, all of the first three detected cases there, presented with rather rare clinical picture (extremely early presence of muscular paralysis, seizures, and/or absence of CSF pleocytosis) in conjunction with lack of detailed description of microbiological approach used to establish the diagnosis, raises suspicion in TBE diagnosis. In the study of Grygorczuk et al, there is some inconsistency in data analysis: 146/152 (96%) patients with TBE were reported to had had raised CSF cell count (normal range not reported), however lumbar puncture was conducted in only 134 patients in the first 24 h and in 9 patients on day 2-7 of hospitalization, that is in 143 patients all together. Nevertheless, the same proportion of patients with lumbar puncture performed in the first 24 h of hospitalization (129/134 = 96%) was reported to had had pleocytosis > 10 x 10^6 cells/l and CSF cell count ranged from 3 to 375 x 10^6/l. However, detailed description of diagnostic procedure to affirm TBE diagnosis in patients without pleocytosis (whether be it < 5 or < 10 x 10^6 cells/l) was not provided in the manuscript. It might be that patients who did not have CSF pleocytosis at the time of the first lumbar puncture exhibited elevated cell count at follow-up examination.
The case report

Comment 2: In the paper the CSF cell count is not given, and not the reference value for CSF cell count used. This is important information to include. This is even more important since the fact that “lack of CSF pleocytosis” also must be defined. This issue is problematic. If for example maximum CSF leucocyte count of 5 x 10E6/L CSF is considered to be within the normal range this means “lack of pleocytosis”. Others use CSF WBC upper limit 10 x 10E6/L. The problem can be made even more difficult if cell types are considered. How many monocytic cells are within the normal range and how many polymorph nuclear cells can be accepted as “normal”? None of these fundamental issues for the understanding of the case report is presented, which is necessary.
Response: We added the lacking information to the manuscript. See Page 4, line 4-5 and line 9-10.

The discussion

Comment 3: The discussion does not correctly describe the history behind the long-standing discussion concerning the definition to be used for reporting TBE cases. The basic problem initiating this discussion was that febrile cases without meningo-encephalomyelitis in several countries constituted a significant part of the reported TBE cases. This difference made comparisons between countries and also between years almost impossible. The need to use CSF pleocytosis as diagnostic criteria was to avoid the inclusion of non-meningoencephalitic cases and allow TBE with neurological diseases to be separated from only febrile, or even subclinical, IgM positive cases which were included in several national reports. In clinical praxis a problematic issue is to differentiate febrile TBE cases with no CSF involvement from the second stage TBE with only light meningitis and without encephalitis. For sure, we must all have made spinal tap and been surprised by the high CSF pleocytosis seen in also very mild cases. This is also the reason why inclusion criteria in several large cohort studies have been CSF pleocytosis, to avoid inclusion of purely febrile cases (first stage disease) and also criticism for including TBE cases without neurological involvement. On the other hand history clearly shows that leaving out clinical cases of encephalitic TBE without CSF pleocytosis, by misunderstanding the clinical criteria in this respect, is numerically a limited problem. Partly due to the unusual occurrence of normal CSF leucocyte count in TBE encephalitis and partly due to the fact that it is accepted to include encephalitis cases without CSF pleocytosis. If obvious encephalitic/myelitis signs and symptoms exist without pleocytosis in CSF IgG sero-conversion is suggested to be required for diagnosis (special considerations also needed for TBE vaccinated with a possible breakthrough). If CSF pleocytosis exists it has been suggested to be enough for fulfilling the diagnostic criteria if cerebrospinal fluid findings compatible with TBE are present together with a positive serum IgM for TBE. In routine clinical praxis at least, this is a very common approach in many countries to simplify the diagnostic process in TBE.

Response: We agree with the reviewer’s comment and amended the manuscript accordingly, however, we thought that the more detailed discussion on TBE definition was beyond the scope of our case report. The main goal of our report was to describe a case of TBE with clinical presentation of central nervous system involvement without CSF pleocytosis but in conjunction with microbiologically proved CNS infection. Therefore our case clearly differs from febrile cases without CNS disease which are being classified as TBE cases for
epidemiological purposes based on serological demonstration of TBE virus infection, and also differs from cases of TBE with neurological involvement because of the absence of CSF pleocytosis.

Comment 4: It is necessary that the discussion take this historic background into account, otherwise the full implications of the fact that CSF non-pleocytotic TBE encephalitis exist will be hard to understand in relation to the proposed diagnostic criteria or change of already proposed criteria. It is also doubtful to say that a general view among initiated TBE clinicians is that no CSF pleocytosis exclude the possibility of TBE encephalitis. This may however, as pointed out, be a misunderstanding among many clinicians seeing TBE patients which needs to be corrected. This also makes this case report worth publishing, but only after substantial revision, correction and updated information.

Response: We would like to thank the reviewer for this and previous comments that enabled us to substantially improve our article. We hope that the new version of Discussion enables a more straightforward understanding of the existence of encephalitis with normal CSF cell count due to TBEV infection, and enables awareness that strict diagnostic criteria are needed for a reliable diagnosis of this entity.

Comment 5: The basis for defining CSF non-pleocytosis should also be shortly mentioned in the discussion. It could also be worthwhile mentioning that TBE is not unique with encephalitic cases seen without CSF pleocytosis, rather that this is a phenomena sometimes encountered, although quite rarely, in viral encephalomyelitis in general irrespective of viral etiology.

Response: We agree with reviewer’s comment and have amended the manuscript accordingly. See Page 4, line 4-5 and line 9-10, and Page 6, line 11-15.