Author’s response to reviews

Title: Immune Mediated Pediatric Encephalitis – Need for Comprehensive Evaluation and Consensus Guidelines

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Author’s response to reviews:

Please see cover letter. Responses are also below.

Editor Comments:

There was an intense discussion with the reviewers and it was recommended that you set the focus on clinical difficulties in this four cases of encephalitis. How far should we go with immunotherapy if we are not sure about the nature of disease?

We very much appreciate your thoughtfulness in the feedback and this opportunity to refocus on clinical difficulties; it is a great point and we added it both in the Abstract and text, particularly in Discussion.
In the Abstract, we have modified the body of Conclusions to read:

“There is a heterogeneous presentation of neuropsychiatric manifestations of autoimmune encephalitis in pediatric populations. In the absence of positive findings on testing, individuals who do not meet proposed criteria for seronegative encephalitis may be misdiagnosed, and/or may not respond adequately to treatment. Pediatric antibody-negative autoimmune encephalitis is particularly poorly understood, which increases the necessity of stringent application of consensus guidelines for diagnosing this condition. In those cases, comprehensive evaluation and stringent application of consensus guidelines is necessary.” – page 1

In the Discussion we have added:

“Despite improvements in diagnostic technology, there are still a significant number of cases of unknown etiology. The diagnostic conundrum of cases presented here is that they all displayed psychiatric symptoms but at the time, their presentation could not be explained by psychiatric diagnosis alone.” – page 11

“…This often poses a clinical dilemma: how aggressive should the treatment be in cases where diagnosis is unclear? In the adult population, the consensus seems to be that aggressive treatment should be considered in most situations due to a high likelihood of favorable outcomes.(21) The data is lacking in the pediatric population and no official guidelines are present. However in light of potential side-effects of immune treatment, autoimmune encephalitis criteria is pragmatically made more stringent when no biomarker or inflammation can be found as in cases of encephalitis of unknown etiology. By contrast, if a known and clinically relevant antibody is identified, the same criteria may be relaxed to provide the necessary treatment for the patient. We specifically chose the cases for this series to outline diagnostic and treatment challenges in the field and to illustrate that ultimately the treatment of these individuals is based on the empirical evidence accrued to the best of ability and is far from definitive at the present time.” – page 11

Since the etiology of these 4 cases remains unclear, please change the background in the abstract/introduction and introduce “encephalitis of unknown etiology”. I also recommend shortening the background to essential information (e.g. shorten treatment of AE).

Thank you for the suggestion. We have introduced the concept of encephalitis of unknown etiology in the Abstract Background and commented on it in the Discussion.
More specifically, in the Abstract under Background we have added: “At least 40% of neuroencephalitis cases are of unknown etiology which adds to difficulties in making the right diagnosis and deciding on the appropriate treatment.(1)” – page 2

In the Background of the text we have added: “Etiology of encephalitis varies depending on different geographic regions with majority of cases remaining unexplained.(5)” – page 3

as well as: “Still, according to a recent systematic review(5), in many cases the causative agent of encephalitis remains unknown, despite advances in laboratory and imaging technology. This might suggest that there are a number of unknown pathogens that have not been associated with encephalitis and/or that some of the immune-mediated mechanisms are not well understood.” – page 3

In the Discussion we added “Despite improvements in diagnostic technology, there are still a significant number of cases of unknown etiology.” – page 11

We have shortened the Abstract Background to essential information on page 2.

We have shortened the section on treatment of AE in Background on pages 3 and 4.

Please put the focus of the manuscript on the diagnostic procedures needed in such ambiguous cases and whether it is appropriate to “challenge” these patients with immunotherapies (risk/benefit discussion). The publication should also have some clear message.

Thank you for this valuable feedback. We have added to and re-organized the Discussion and hope that this allowed for a clear message.
In the Discussion we write: “Use of clinical guidelines, applied in a systematic way, might have been helpful in the care of these patients. For example, although negative autoantibodies do not preclude definitive diagnosis of autoimmune encephalitis, they can be useful for determining subtype, treatment choice, and prognosis.(16) Additionally, when managing an autoantibody negative case, further testing should be considered as per the consensus guidelines, and this should always include CSF if serum is negative. Confirmatory tests should be strongly considered, such as cell-based assay and tissue immunohistochemistry.(16)” – page 11

Additionally, in the Discussion the following paragraph has been relocated to better emphasize the risk/benefit discussion: “Weighing the risks and benefits of treatment requires an evaluation of the patient’s functional impairment, side-effects,(29) the reasonable safety profile of IVIG (30) and other treatment options, and the risk of progressive decline in the absence of treatment. Improved outcomes have been associated with immunotherapy, early initiation of treatment, and use of second and third-line treatments if necessary.(31)” – page 11

The above risks/benefits paragraph then leads to our new discussion of the clinical dilemma of how aggressive should treatment be when diagnosis is unclear (page 11 in the manuscript and above).

It should already be made clear in the abstract (and probably title) that there is a „need for a comprehensive evaluation with use of consensus guidelines for diagnosing seronegative autoimmune encephalitis.“

Thank you for this important feedback.

The title has been changed to “Immune Mediated Pediatric Encephalitis – Need for Comprehensive Evaluation and Consensus Guidelines” – page 1

Additionally, we have added the following to Abstract Conclusions: “In those cases, comprehensive evaluation and stringent application of consensus guidelines is necessary, alongside careful treatment planning.” – page 2
Is serum left from these patients to test again by IHC in a brain tissue or a neuronal cell culture as suggested by reviewer 3?

Unfortunately there is no serum left from these patients. We appreciate your thoughtful suggestion.

We clarified the lack of tissue testing in the text at the end of Background: “These cases were diagnostically challenging, with negative autoantibody panels, normal or inconclusive MRI results, non-specific CSF changes, and no tissue testing (either via immunochemistry in brain tissue or a neuronal cell culture).” – pages 4/5

Reviewer reports:

Ming Lim (Reviewer 2): In the revision, the authors have addressed the concerns raised by reviewers to the best of their ability. It makes a more balanced overview of a true problem the clinician faces.

We thank you for your thoughtful comments. The goal of our case series was to show real world issues that clinicians face and we are glad to hear it is a more balanced overview.

I only have three suggestions. Firstly, I think important for "immune mediated" to be added to title.

The title has been changed to “Immune Mediated Pediatric Encephalitis – Need for Comprehensive Evaluation and Consensus Guidelines” – page 1

Secondly, I think they should make important point that in light of potential side-effects of immune treatment, AE criteria is pragmatically made more stringent when no biomarker of inflammation can be found; and by contrast can be relaxed if a known clinically relevant antibody is identified. Ultimately the treatment if these groups of patients are based on the empirical evidence accrued to the best of ability and is far from definitive currently.
Thank you for this wonderful suggestion.

We added the following in the Discussion:

“This often poses a clinical dilemma: how aggressive should the treatment be in cases where diagnosis is unclear? In the adult population, the consensus seems to be that aggressive treatment should be considered in most situations due to a high likelihood of favorable outcomes.(21) The data is lacking in the pediatric population and no official guidelines are present. However in light of potential side-effects of immune treatment, autoimmune encephalitis criteria is pragmatically made more stringent when no biomarker or inflammation can be found as in cases of encephalitis of unknown etiology. By contrast, if a known and clinically relevant antibody is identified, the same criteria may be relaxed to provide the necessary treatment for the patient. We specifically chose the cases for this series to outline diagnostic and treatment challenges in the field and to illustrate that ultimately the treatment of these individuals is based on the empirical evidence accrued to the best of ability and is far from definitive at the present time.” – page 11

Finally, I think the cases reported do not allow them to make a conclusion of wide spectrum of neuropsychiatric manifestation of AE. Instead, it should be reformulated as that there is heterogeneous presentation of neuropsychiatric features in children whereby an autoimmune (or immune-mediated) aetiology should be investigated with well established guidelines but that management is difficult and not definitive when no biomarker (define perhaps) can be identified.

We have edited Conclusions in the text to reflect your excellent suggestions:

“There is a heterogeneous presentation of neuropsychiatric features of autoimmune encephalitis in pediatric populations. Since patients with autoimmune encephalitis often present with physical and psychiatric symptomatology, psychiatrists and neurologists are both commonly involved in their care. Cases with negative autoantibody panels, normal/inconclusive MRI results, and non-specific CSF changes, but with clinical symptomatology suggestive for autoimmune encephalitis are difficult to manage and not definitive when no biomarker can be identified. There is a need for comprehensive evaluation with use of consensus guidelines for diagnosing seronegative autoimmune encephalitis.” – page 12
We have also edited the Conclusions in the abstract to read:

“There is a heterogeneous presentation of autoimmune encephalitis in pediatric populations. In the absence of positive findings on testing, individuals who do not meet proposed criteria for seronegative encephalitis may be misdiagnosed, and/or may not respond adequately to treatment. Pediatric antibody-negative autoimmune encephalitis is particularly poorly understood, which increases the necessity of stringent application of consensus guidelines for diagnosing this condition. In those cases, comprehensive evaluation and stringent application of consensus guidelines is necessary.” – page 2

Ilya Ayzenberg (Reviewer 3): ... Taking altogether, despite true that a diagnosis of a seronegative autoimmune encephalitis in children (and adults also) is challenging, the main message of the publication as well as a final diagnosis in described cases remain unclear (treatment effect was also not helpful, tissue tests not performed).

Probably a clear positive IHC in a brain tissue or more specifically in a neuronal cell culture would be helpful to confirm an autoimmune nature of some of cases. In that case further clinical analysis of seronegative and in-tissue/culture positive cases could be interesting.

Thank you for your comments and taking the time to read and evaluate our paper. We edited our manuscript to clarify the main message of the publication.

Unfortunately there is no serum left from these patients. We clarified the lack of tissue testing in the text at the end of Background: “These cases were diagnostically challenging, with negative autoantibody panels, normal or inconclusive MRI results, non-specific CSF changes, and no tissue testing (either via immunochemistry in brain tissue or a neuronal cell culture).” – pages 4/5

We agree that further clinical analysis would be very interesting and appreciate your thoughtful suggestion.