Author’s response to reviews

Title: Longitudinal brain morphology in anti-NMDA receptor encephalitis: A case report with controls

Authors:

Heikki Laurikainen (heikki.laurikainen@utu.fi)
Iina Isotupa (iiemis@utu.fi)
Mikko Nyman (mikko.nyman@tyks.fi)
Tuula Ilonen (tuuilo@utu.fi)
Teija Nummelin (teija.nummelin@tyks.fi)
Raimo Salokangas (raimo.k.r.salokangas@utu.fi)
Jarmo Hietala (jahi@utu.fi)

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Author’s response to reviews:

We thank the reviewers for the constructive criticism. We have reviewed the suggested literature and updated the introduction section accordingly; answered questions pertaining possible confounding factors of volumetric changes; addressed and clarified questions about assessment and characterization of neurologic symptoms; and corrected suggested errors in formatting and nomenclature. We hope that the revised version of the case-report can be published in the BMC Psychiatry. We have addressed the criticism point-by-point in the following:

Reviewer reports:

Shekeeb Mohammad (Reviewer 1):

Comment 1: The authors have submitted a case report of a young adult with anti-NMDAR encephalitis who was noted to have volume reduction in the frontal regions of the brain on analysis of follow up MR imaging though there was no difference acutely and no obvious difference on conventional appearance of MR imaging. The single case report reiterates a non specific appearance that may be apparent after an acute brain inflammatory condition. The appearance on imaging (conventional and non conventional) in patients with NMDAR encephalitis has been increasingly described.

Answer 1: It seems reasonable to assume that the presented frontal volume loss could be due to non-specific causes present in general acute brain inflammation. However, the literature does not
support this assumption in anti-NMDAR encephalitis since localized atrophy is reported as a relatively infrequent finding. We would also like to emphasize that there are very few longitudinal MRI studies on anti-NMDAR encephalitis using exactly the same MRI sequences and the same scanner. We feel that this is a strength in this case-report but fully acknowledge that studies on larger patient samples are needed.

Comment 2: The finding from the single case report may well be due to medication effects, particularly from use of immunotherapy and the design of the controls described does not help discriminate this.

Answer 2: We completely agree. Even if causal inferences were possible, generalizations could not be made from a singular observation. This is an obvious common problem in studies on severe conditions such as anti-NMDAR encephalitis where controlling for e.g. drug effects is difficult. We have tried to communicate this restriction that medication effects cannot be ruled out to the reader in the discussion, page 10, line 276-277: “The volumetric changes could also be due to psychiatric or immunological medication effects”, and page 11, lines 280-281. Further, the importance of persistently elevated antibody levels despite good functional outcome is emphasized by this notion of possible iatrogenic effects. The administration of rituximab was justified in this case presentation by elevated antibody levels, and on retrospect the levels didn’t seem to be associated to poor functional outcome. We feel that communicating this dissociation, and possible pitfalls to guiding clinical practice based on antibody levels, is valuable to clinicians. Accordingly, we have modified the discussion regarding iatrogenic effects to emphasize it to the reader (discussion, page 11, lines 285-288).

Comment 3: The literature review and referencing is quite out of date and I would recommend that authors were to go through this in further detail particularly the following key papers:

2015 Heine et al. http://dx.doi.org/10.1016/j.neuroscience.2015.05.037
2015 Finke et al. http://dx.doi.org/10.1016/j.biopsych.2015.02.024
2018 Bacchi et al. https://doi.org/10.1016/j.jocn.2018.03.026
2018 Wang et al. https://doi.org/10.1007/s00415-017-8707-5
2018 Zhang et al. http://dx.doi.org/10.3174/ajnr.A5593

Answer 3: We thank for these very useful references. Still, there are very few methodologically rigorous follow-up MR studies on this patient population and the longitudinal change in morphology is the key point of this case-report. Anyway, we have updated the introduction section to provide to the reader a more thorough analysis of the relevant imaging literature. Specifically, we updated the numbers on the proportion of patients with findings in structural
MRI (introduction, page 3, line 95), added more detailed information about the nature and location of typical structural changes (introduction, page 3, lines 97-101), and added that frontocortical volume loss seems to not have been described in a longitudinal design using volumetric analysis (introduction, page 4, line 102). We have also added a description of whether imaging findings associate to functional outcome or cognitive changes (introduction, page 4, lines 105-110). We feel that these additions underline the relevance of communicating this case report.

Tüzün Erdem (Reviewer 2):

Comment 1: The presented case demonstrates that in a NMDAR encephalitis case with a relatively favorable outcome and no relapse, minor permanent neuronal loss may occur emphasizing the importance of early diagnosis and treatment. This is an interesting and novel observation and the case presentation fills a gap in the field of autoimmune encephalitis.

Answer 1: We also feel that the presented frontocortical volume loss in the absence of findings in routine radiological assessment, but also the fact that good functional recovery was achieved although antibody levels remained elevated after rituximab treatment, contributes novel observations to the field.

Comment 2: Authors would probably have done a better job if they had shown the progress of volume alterations in multiple brain regions by performing measurements of several successive MRIs between baseline and 9 months. In that case they could also provide absolute values rather than percent change values.

Answer 2: Additional structural measurements both before, within and after the presented timepoints would have provided valuable information about the temporal course of structural changes. Added temporal resolution might have even made inferences about the factors behind volume loss, e.g. medications, possible. Unfortunately, the method used here for volumetric analysis requires the use of the very same MRI scanner and scan parameters in all timepoints for all subjects. This data was available only at the reported time-points. We have added more detailed information of the used scanner and scan sequence parameters into the supplementary methods in supplementary file 1.

Comment 3: The statement "Extrapyramidal and motor symptoms continued to worsen nevertheless" sounds vague since before this statement there is no mentioning of baseline neurological examination and somatic neurological problems of the patient. This information should be provided. What does joint stiffness precisely refer to? Rigidity?, parkinsonism? Or something else?

Answer 3: The case did not suffer from lifetime neurological or neuropsychiatric illness prior to admission. We have clarified this to the reader in the case description, page 8, line 203. We also
corrected the term “stiffness” to “rigidity” in the case presentation (page 6, lines 167-168), since it is a more exact expression of the presentation. The neurological status of the case was evaluated at admission with routine clinical examination, but also in the context of a prospective first episode psychosis study including systematic evaluation of elbow rigidity, tremors and gait, using a subset of neurological examinations included in the Simpson-Agnus scale. Since the subsequent observations of extrapyramidal symptoms were made by the treating physicians we do not have the possibility to provide exact measures or time-course of change from baseline, nor to quantify to what degree the symptoms continued to worsen. However, we have tried to make it clear that this case, who had been previously free of neurological illness, progressed into a mixed array of neurological symptoms despite discontinuation of possible contributing medications. We have attempted to describe the nature and course of neurological symptoms accurately but acknowledge the ‘soft data’ nature of the EPS findings.

Comment 4: I would consider including modified Rankin scores at admission, discharge and at the time of worst neurological symptoms (maximum mRS).

Answer 4: Using mRS would definitely facilitate cross study evaluation of study populations since a large proportion of studies on anti-NMDAR encephalitis have used mRS. The presented case was identified as a potential participant of a prospective first episode psychosis cohort study, which included serial assessments of functioning using the global level of functioning (GAF) scale. We feel that GAF is more justifiable than the mRS in this case since the latter would have to be a retrospective evaluation. Also, as a general measure of function the mRS does not capture subtle deficits, including moderate cognitive dysfunction, which might have still been present. This patient attained good functional recovery and mRS would not be as sensitive to minor residual symptoms of functional disability as the measures provided in this case (GAF, neuropsychological and psychiatric evaluation).

Comment 5: Could ECT, rather than autoimmune encephalitis, have caused late onset neuronal loss? Please discuss this possibility.

Answer 5: This is a relevant point. The patient received 3 sessions of electroconvulsive therapy (ECT), which in the context of major depressive disorder, catatonia and psychotic disorders is certainly considered a subtherapeutic dose. The timing of ECT was over six months before follow-up MRI. We are not aware of any publications about the use of ECT in anti-NMDAR encephalitis. However, extensive literature about morphological changes after ECT in psychiatric disorders is readily available. ECT should rather increase cortical volume as measured with MRI than cause atrophy. Thus, it seems improbable that ECT would have had a major contribution to the effect described here. To clarify this to the reader we have added a discussion on this topic in the discussion on page 11, lines 281-284.

Comment 6: Please type methylprednisolon as "methylprednisolone"
Answer 6: Thank you for pointing this out. We made the correction to the case presentation, page 7, line 188.

Comment 7: In the abstract atypical should be typed as "a typical"

Answer 7: The clinical presentation of the case can be described as typical. However, the dissociation of functional outcome and antibody levels/frontocortical volume loss cannot be described as typical or atypical in light of the currently available literature. We chose to remove this unclear and possibly not very useful characterization from the abstract, page 2, line 66.