Author’s response to reviews

Title: The MRZ reaction helps to distinguish rheumatologic disorders with central nervous involvement from multiple sclerosis

Authors:

Tilman Hottenrott (tilman.hottenrott@uniklinik-freiburg.de)
Rick Dersch (rick.dersch@uniklinik-freiburg.de)
Benjamin Berger (benjamin.berger@uniklinik-freiburg.de)
Dominique Endres (dominique.endres@uniklinik-freiburg.de)
Daniela Huzly (daniela.huzly@uniklinik-freiburg.de)
Jens Thiel (jens.thiel@uniklinik-freiburg.de)
Sebastian Rauer (sebastian.rauer@uniklinik-freiburg.de)
Oliver Stich (oliver.stich@uniklinik-freiburg.de)
Ulrich Salzer (ulrich.salzer@uniklinik-freiburg.de)
Nils Venhoff (nils.venhoff@uniklinik-freiburg.de)

Version: 1 Date: 16 Sep 2017

Author’s response to reviews:

Dear Prof. Patti,

Thank you very much for the helpful and very valuable comments which helped us to further improve the manuscript. In the following we respond to the outstanding queries providing a 'point-by-point response' to both reviewers:

Reviewer #1:

Comment 1):

The authors should add the data about the interval between clinical onset and time of LP and comment on correlations between duration of this interval and MRZ data.

Response to 1):
We agree to that issue and added the respective data regarding the disease duration (defined as the time interval between clinical onset and time of LP) of all patients; and calculated the correlation between the disease duration and MRZ result in all patient groups using the point biserial correlation analysis (two-tailed). We added the following sentences to the respective sections:

“There was no significant correlation between the disease duration and the MRZR result of patients in all three study groups (RDwCNS: rpb -0.19; MS: rpb +0.18; OIND: rpb +0.19; p > 0.05 for all groups).”

“The similar age and disease duration of MS and RDwCNS patients are advantages for interpretation of their MRZR results since these items may have an effect on the prevalence of positive MRZR outcomes. Indications for this are the lower prevalence in paediatric compared to adult MS patients and increasing prevalence within the individual disease course [Reiber 2009, Petereit 2005]. However, in the present study there was no correlation between the disease duration and the MRZR result of all patients irrespective to their diagnosis group.”

Comment 2):

Have the authors any information about the possible bias that LP is usually performed after or during a clinical attack? Any longitudinal data on MRZ indices?

Response to 2):

This is an interesting point (see also response to comment 1); but unfortunately we do not have or know sufficient data to properly address this bias. One reason might be that the vast majority of CSF data derives from LPs performed shortly after or during the presence of clinical symptoms. To our knowledge the only longitudinal data regarding MRZ was reported in this study:


Briefly, in 70 patients a positive MRZR-2 was found in 63%; but in the follow-up LP (after a mean time of 22 months (range 1-106months)) 79% were MRZR-2 positive. Thus, the prevalence of a positive MRZ seems to slightly increase over time. A possible reason for that might be “an expanding B cell activity during the course of the disease” based on “CSF analysis in which the prevalence of mature plasma cells was found to be higher in patients with longer disease duration”.

Comment 3):

Have the authors analyzed the correlation between the number of OCB/IgG index and MRZ?
Response to 3):

No, this was not possible as we do not assess the exact number of OCB and did not have the IgG index of all patients. In our clinical routine OCB are evaluated only semi-quantitatively according to the consensus report “Cerebrospinal fluid in the diagnosis of multiple sclerosis.” (Andersson et al. J Neurol Neurosurg Psychiatry. 1994) using the Wurster patterns I – V. But it is a very interesting idea to correlate the IgG index with the MRZ in a future study.

Comment 4):

The authors should point out the usefulness of a comprehensive evaluation in any single patient with inflammatory CNS involvement considering clinical, multiple systemic and CSF biomarkers, as well as Neurophysiological and MRI data.

Response to 4):

We agree to that recommendation and added the following sentences to the discussion section:

“In every patient with a suspected inflammatory CNS affection the comprehensive evaluation of all clinical, blood and CSF biomarkers, as well as neurophysiological and MRI data is indispensable. If diagnostic uncertainty then still persists, a biopsy should be considered in case of a significantly affected patient and if the exact diagnosis is relevant to the choice of the therapeutic drug.”

Reviewer #2:

Comment 1):

The retrospective study has not evaluated the autoantibodies in the MS people and these data could be interesting to know, because, as the authors themselves state, the ANA can be found in about 30% of MS people.

Response to 1):

This is a very valuable comment which helped to further enhance the content of our study. We added the data (derived from medical records) regarding the prevalence of autoantibodies of the MS patient group to the respective manuscript sections. We added the sentence to the results section:

“Thirty-six MS patients were screened for ANA and 50.0% showed a positive result.”

Comment 2):
Have the authors evaluated the sample distribution?

Response to 2):

Thank you for this very important issue we had not properly addressed for all parameters. Therefore, we analysed the sample distributions using the Kolmogorov-Smirnov test with the following results:

Mean age:

- RDwCNS group (n= 23; mean= 44.83; sdev= 17.2): “the data is consistent with a normal distribution: P= 0.58 where the normal distribution has mean= 46.25 and sdev= 17.53”.

- MS group (n= 46; mean= 43.91; sdev= 15.8): “the data is consistent with a normal distribution: P= 0.30 where the normal distribution has mean= 45.04 and sdev= 15.00”.

- OIND group (n= 48; mean= 51.77; sdev= 18.6): “the data is consistent with a normal distribution: P= 0.78 where the normal distribution has mean= 50.56 and sdev= 20.76”.

But mean AI and mean disease duration (see comment 1 of Reviewer 1) were unlikely to be normally distributed according to the Kolmogorov-Smirnov test. Thus, we (re)calculated the respective group comparisons using the Mann-Whitney U test (two-tailed) without any significant changes (all significant results remained significant and vice versa). Respective results were shown in tables 1 & 2.

Comment 3):

The contrast enhancement in MRI is performed using the sequences in T1. The text has to be modified according to this (e.g. the line 305).

Response to 3):

We changed the respective words into: “…T1 lesions with contrast enhancement…”.

Comment 4):

Another limitation of the study, as the authors recognise, is the low number of people, which means it's not possible to generalise the results.

Response to 4):

We completely agree to that comment and tried to address that issue by adding this part to the respective sentence: “…which reduce the generalizability of the present study results.”