Author's response to reviews

Title: Is a hypothetical melanoma-like neuromelanin the underlying factor essential for the clinical manifestation of multiple sclerosis?

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Author's response to reviews:

Dear editor Josefino M Rodis,

We are grateful for your and the reviewer’s comments and have responded appropriately:

Reviewer: Amanda Waddell
Reviewer's report:
Minor essential revisions
1) In the section, MLN might explain the relevant mode of action of diverse factors in the aetiology of MS, the first paragraph with questions about T cell function is not written in a way to make an obvious connection to MLN. I think this paragraph should be rewritten to make the connection more apparent within the paragraph.

We have rewritten the section ‘Underlying virological factors in the biogenesis of MLN’ to link altered intracellular redox potential to syncytin-1 overexpression which, in turn, is linked to HERV overexpression induced by altered T cell activity.

Discretionary Revisions
1) How pathological neuromelanin could be generated is explained, but a figure showing how this may occur, with drawings of chemical structures, could be helpful

A figure has been added and a small new Table 2.

Reviewer: Vladeta Ajdacic-Gross
Reviewer's report:
This contribution discusses the eventual role of a hypothetical melanoma-like neuromelanin in the etiopathogenesis of multiple sclerosis. The authors propose to search for a single factor, i.e. a unifying concept, essential in the clinical manifestation of MS.

The manuscript brings together a large number of findings and results from different disciplines participating in MS research. From this perspective, this is a
courageous paper. It stands out from the bulk of specialized contributions and authors who are not able to take notice of findings outside their small world. Nevertheless, I think that the authors could improve their contribution substantially.

Major Compulsory Revisions

1. In general, the manuscript is not clear and straightforward enough. An obvious obstacle is that the authors should avoid including issues that do not pertain to the specific chapters or to the manuscript itself, for example:
   • discussion on prevention at the end of the article (even though I fully agree with their notions on a vaccine against EBV)
   We have altered the end of the article to emphasize the difference between prevention (which the reviewer and we agree could well be a vaccine against EBV) and therapy of established MS.
   • second paragraph on p. 7, which does neither refer to MLN nor to the chapter on the whole
   We have rewritten the relevant parts of the text to focus on those aspects of MS that we consider to be directly related to MLN.

2. Basically, it is not clear whether the authors consider the hypothetical MLN as clinical manifestation factor (title) or as a factor relevant during earlier stages of etiopathogenesis (second paragraph, p. 15). Provided that MS etiopathogenesis is a multistage process, the authors might prefer to denominate explicitly and earlier in the text their underlying model and the stage(s) where they assume MLN to be relevant.
   We have altered the title and text to emphasize that, while the many putative factors in MS appear to be essential at various stages of the course of the disease, we postulate that MLN is involved throughout.

3. Second, since the manuscript is speculative, the authors might aim to clearly distinguish between, first, the trustworthy basis of a specific argumentation, between the different options which may be derived on a second level, and, on a third level, the related outcomes or prognoses which may result from the options and could be compared or eventually tested. It should be clear for the reader, which parts of the text relate to the knowledge basis, which one to alternatives and which one to speculative notions.
   We have made the strength of the evidence clear in the text and Table 1.

4. Third, and in analogy with the second issue, the authors might choose to filter and to weigh the reported findings and not favour their quantity. Unfortunately, many findings in MS research have been short-winded, and many mechanisms are of superficial generality (for example, there are thousands of oscillatory or aging processes that might interfere more or less exactly with MS etiopathogenesis). Typically, the strength of arguments varies tremendously.
   We have attempted to do this, in the same manner as for point 3 above.

Discretionary Revisions
Finally, I wondered about the role of a hypothetically unifying concept such as MLN within the framework of a hypothetically heterogeneous disease such as MS. Perhaps, the author might comment on this.

We have added the comment that as the many other putative factors implicated in the pathogenesis of MS vary from region to region, from time to time and from patient to patient, the involvement of MLN could be a constant feature despite the heterogeneous nature of the disease.

Informations in old Tables 1 and 2 were combined in new Table 1, old Table 3 is deleted.

Yours sincerely, Bernd Krone