Reviewer's report

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

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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)

• second paragraph on p. 7, which does neither refer to MLN nor to the chapter on the whole

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.

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.
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.

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.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.