Reviewer’s report

Title: MS in South Asians in England: early disease onset and novel pattern of myelin autoimmunity

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Reviewer: Volker Siffrin

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In this manuscript Nicholas et al. investigate a monocentric study population of Caucasian vs. S.Asian MS patients and controls in the the UK. They analyzed the clinical manifestation and the T cell antigen recognition pattern between patients or controls. They describe that S.Asians are significantly younger than Caucasians at the onset of the disease. In addition, they found distinct pattern of myelin peptide antigen recognition in the different groups. They claim that these differences might reflect different exposure to environmental risk factors which might be used for diagnostic and therapeutic purposes.

In general, the question why immigrants and in particular the second generation have a higher incidence of western type MS has been pressing for decades and still has not been answered satisfactorily. It is also interesting to correlate these epidemiologic findings with immunological investigations. However, I have concerns about the quality and the statistical analysis of the data in the presented study.

Major Compulsory Revisions

1) I have clearly problems to understand the recruiting strategy of this study. There is no clear statement in the methods. Were all patients included that were treated with a first episode that were treated within a certain period at the same clinic? If not, why is there no matching for age (the Caucasian MS patients being significantly older?) Or were there other selection criteria to chose these patients in this study?

2) The authors do not discuss any possible confounding effects for the observed earlier onset of the disease in S.Asian vs. Caucasian patients. It might well be that the late-onset S.Asians are not observed because of different numbers of immigration (more immigrants in the 1970ies than in the 1950ies excluded?). It seems to me that this observation needs more consideration and that the conclusion is taken too fast that S.Asians have earlier MS in the UK.

3) Is the effect in Fig. 2 really specific for myelin peptides? Have they done a control with a non-myelin peptide, e.g. tetanus toxoid or birch pollen. Can the authors exclude that some patients are more prone to IFN-g production than others? Did they check if e.g. proliferation showed a similar pattern?

4) I have serious concerns about the presentation and the statistical analysis of the T cell reactivity data as presented in Fig. 3 and 4. First, the graphical representation is not sufficient. It is hardly possible to recognize anything in these
figures due to the size and the lack of a legend. Furthermore, the strength of a mean antigen response would be more informative than the percentage of claimed positive responses. It would to my understanding make more sense to show a stimulation index (x times baseline value). In addition, statistical analysis should be done over all epitopes.

Minor Essential Revisions
5) The discussion lacks the appraisal of epidemiologic data from the 1960ies/70ies concerning MS risk and migration. Here, several potential confounding factors have been described for e.g. younger age at onset.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I have no competing interests