Reviewer’s report

Title: Cortical injury in multiple sclerosis; the role of the immune system.

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Reviewer: Hans Lassmann

Reviewer’s report:

This is a very well written review on an interesting and important topic, the importance of cortical lesions in multiple sclerosis and their relation to inflammation. The review summarizes in a concise manner, what is currently known in relation to this topic and it provides a balanced account on previous work in this area. There are, however, a number of points, which need to be addressed before publication:

1) Page 3: The authors got mixed up with the historic dates. Charcot published his work not before but 30 years after Carswell. In addition, Carswell described spinal cord but not cortex. He indicated affection of the spinal grey matter, but not of cortex.

2) Page 5: EAE models with cortical demyelination: The Merkler model is certainly not unique. There are papers on cortical demyelination in EAE models, which describe cortical demyelination in depth (Pomeroy et al Brain 2005; Storch et al JNEN 2006). It may be interesting to not that in all these EAE models cortical demyelination invariably depends upon demyelinating antibodies and complement, which does not seem the case in (at least the large majority) of cortical MS lesions.

3) The authors point out at several occasions that cortical demyelination in progressive MS lacks inflammation. This is a bit too dogmatic. The problem there is that in the original studies of the Amsterdam group cases have been described with very little or (in most cases) absent ongoing active demyelination. In these cases there was no inflammation and BBB damage. The major problem related with these studies is that stringent criteria for active cortical demyelination (such as the presence of recent myelin degradation products in macrophages/microglia) were not applied. When more active lesions are analysed, more inflammation can be seen (not only in the meninges), but inflammation is still much less pronounced than in the white matter.

4) Similarly the separation between folicle positive and negative cases seems a bit too dogmatic. There is a gradient of meningeal inflammation from absent to moderate and diffuse to the formation of aggregates (folicle like) and this gradient is also reflected in the severity of active demyelination and tissue damage.

5) Meningeal inflammation has not been first described in 1933, but much earlier (between 1900 and 1930). A particularly nice example is Marburg 1906.

6) The reference to the Derfuss paper is misleading. It does not describe that damage to an adhesion molecule disrupts BBB. What it shows is that a T-cell
immune reaction against a neuronal/glia contact molecule may induce inflammation preferentially in the grey matter. In addition the authors did not transfer CD8+ but CD4+ T-cells.

7) In the conclusions the authors ask the question, why there is a resolution of inflammation when the disease moves from the relapsing to the progressive stage. This is actually not the case. In fact, profound inflammation is seen in the brains of patients with progressive disease, at least as long as the disease process is active (see Frischer et al Brain 2009). It seems, however, that in the progressive phase inflammation becomes at least in part trapped behind a partially repaired BBB, which may explain lack of enhancing lesions and therapeutic success.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.