Reviewer’s report

Title: Venous endothelial injury in central nervous system diseases

Version: 1 Date: 1 March 2013

Reviewer: Hans Lassmann

Reviewer’s report:

In this review the authors discuss evidence and mechanisms for venous injury in multiple sclerosis. The authors describe in detail previous studies from their group and from others on clinical aspects, imaging, immunological alterations and genetic factors, which may point to abnormalities in venous blood flow in MS lesions and how such changes could be related to disease mechanisms. They summarize their findings in a figure, which suggests a primary role of venous flow disturbances in the pathogenic cascade of MS lesions.

It appears that this is a biased view. It is known form more that 50 years that inflammation in the brain always starts around veins and venules and in autoimmunity and infections in experimental models this occurs in the absence of any primary venous flow disturbance. Thus all the molecular and immunological changes discussed here may just be due to the inflammatory process and there is no clear evidence presented, which supports the presence of a primary venous insufficiency in MS lesions. There are additional arguments which speak against the authors concept. As correctly described by the authors none of the conditions of well documented venous flow disturbance in humans results in an MS like inflammatory demyelinating pathological phenotype. The authors argue that additional genetic factors may play a role and discuss a number of candidate genes, but currently available data from the GWAS showed no evidence that such genes are associated with MS risk. If they are really important, this would have been seen in the respective GWAS studies. Finally, the only way to substantiate the claim for a primary venous insufficiency as a driving force of MS lesions is to show that CCSVI is really present in MS patients, that it is present at earliest disease stages, that this is not the case in other control conditions and that therapeutic correction is really beneficial. Despite extensive international efforts performed during the last years this has not convincingly be shown.

Quality of written English: Acceptable

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

Declaration of competing interests:

No competing interests