

Pathobiology of MS: complex interplay between degeneration and inflammation

Schenk, G.J., Klaver, R., Klauser, A., Tsutsui, S., Poon, K., Van Minnen, J., Stys P.K., and Geurts, J.J.G.

VU University Medical Center, Dept. of Anatomy & Neuroscience, Div. of Clinical Neuroscience, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands. g.schenk@vumc.nl

Research question and background

Multiple sclerosis (MS) is historically considered to be a prototypical autoimmune inflammatory disease of the central nervous system, with a primary immune assault aimed at myelin and oligodendrocytes. In addition to the well described inflammatory demyelinating pathology, progressive axonal degeneration, and more recently gray matter atrophy, have been emphasized as additional important factors that lead to permanent and progressive clinical disability. It is presently unclear whether autoimmune inflammation triggers MS, or if an underlying degenerative process drives the chronic injury. Conditions that cause axonal degeneration often lead to changes in the accompanying oligodendrocytes, and vice versa. In the central nervous system, myelin defects may result in significant axonal compromise or degeneration, even without initial demyelination. The mechanisms involved in this crucial interdependence of neurons and myelinating cells and their involvement in the plasticity of the brain during MS are the focus of our research.

Methods and tissues used; Results and conclusion

Three research lines have been running for the last years to gain more insight in the complex interplay between degeneration and inflammation in MS:

- 1) Samples of 6 chronic MS cases were fixed in glutaraldehyde and these were investigated using electron microscopy for glial-axonal ribosomal transfer and Myelin thickness. Two publications based on the results are currently in preparation. Collection of additional NAWM and lesion glutaraldehyde fixed samples is ongoing for future investigations.
- 2) To examine myelin status in areas of ongoing de- and remyelination Coherent anti-Stokes Raman spectroscopy (CARS) and multiphoton imaging of white and grey matter lesions were applied. One SPMS, 4 PPMS and control cases were used for this purpose. The manuscript is in preparation.
- 3) To assess which proteins may play a role in oligodendrocyte-neuron interactions in the specific lesion sub-areas we have used a proteomics approach. Five frozen PPMS cases were selected to perform laser micro-dissection experiments, collecting various samples from chronic active white matter lesions. Experiments were successful and data acquisition and statistics are now complete. Several validation experiments will follow, using the paraffin mirror blocks of the 5 PPMS cases used for the laser micro-dissection.