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The eye as a window to the brain: Histopathological assessment of optic nerve pathology in multiple sclerosis

Autor: Sophia Schwarz
Institut / Klinik: Neurologische Klinik
Doktorvater: Prof. Dr. L. Schirmer

In this work, 48 snap frozen optic nerve tissue samples from 2/3 multiple sclerosis patients and 1/3 control patients have been analysed using chromogenic and fluorescent immunohistochemistry as well as duplex and multiplex *in situ* hybridization. First, optic nerves were characterized by the presence of demyelinated lesions, their extent, localisation, and inflammatory activity. Most of the examined optic nerve cross-sections showed a lesion, the extent varied from 15% to 82% of the cross-section surface. Most lesions showed a subpial location indicating an infiltration of immune cells via the meninges. Regarding their inflammatory activity, the lesions could be mainly classified as active or mixed active/ inactive. Next, the focus was set on glial cell diversity. Upregulation of *CD163*$^+$ activated myeloid cells such as microglia and *CD44*$^+$ reactive astrocytes was observed – most pronounced in the peri-plaque white matter, underlining the importance of this area bordering the actual lesion. Glial cell diversity was assessed via multiplex *in situ* hybridization of *GPNMB*, *CD163* and *DOCK8*. Moreover, crosstalk between microglia and astrocytes could be shown with multiplex *in situ* hybridization of *GPNMB* and *CD44*. Regarding the adaptive immune system, increased levels of B and T lymphocytes could be shown in MS meningeal and perivascular tissue. Besides the inflammatory aspects, light was shed on neuroaxonal changes associated with optic neuritis in the context of multiple sclerosis. Axon assessment showed a widespread reduction of the density of healthy axons in multiple sclerosis lesion and non-lesion areas. Furthermore, selective drop-out of small, calibre axons could be observed suggesting a size-selective vulnerability of small axons. Noting that the axons in the optic nerve derive directly from the retinal ganglion cells, they can also retrogradely be affected by axonal injury. Retinal thinning and loss of retinal ganglion cells are often associated with multiple sclerosis and can be measured by optical coherence tomography. Due to a correlation between gene variations of complement factor C3 and retinal thinning that has been described recently, the presence of C3 was examined in the optic nerve tissue. A high expression in multiple sclerosis optic nerve tissue, especially in normal-appearing white matter, an increased expression in *CD44*$^+$ astrocytes and a correlation of *C3* expression with reduced axon density could be shown.