Chapter A3

HISTOPATHOLOGY OF EAE

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Abstract: This chapter reviews the histological structure of the normal central nervous system and the basic pathology of inflammation and demyelination of this tissue. An outline of the pathogenesis of experimental autoimmune encephalomyelitis (EAE) is given and pathology of multiple sclerosis is reviewed. The limitations of EAE as a model for multiple sclerosis are discussed. The approach to histopathological assessment of the lesions of EAE is outlined, including collection and processing of appropriate samples and a review of grading systems that have been used to quantify the histopathological changes. The specific histopathological features of EAE are described with reference to selected model systems including the SJL/J, C57Bl/6 and NOD mouse, the Lewis rat, rhesus monkey and marmoset.

Key words: EAE, multiple sclerosis, histopathology, inflammation, demyelination

1. BASIC MICROANATOMY OF THE CENTRAL NERVOUS SYSTEM

The central nervous system (CNS) comprises the brain, spinal cord, optic nerve and retina; the latter structures considered embryological extensions of the brain. Within the CNS, the broadest structural division is into the myelinated axons of the white matter tracts, and the collections of neuronal bodies, glial cells and surrounding neuropil that comprise the gray matter.

The basic cellular unit of the CNS is the neuron. The neuronal cell body typically receives input from the dendrites that emanate from the cell body, and transmits output along a single axon through the axonal
telodendritic branches to the dendrites of other neurons. The terminal bulbs of the telodendritic branches store neurotransmitter substances that are released into the synapse. Most synapses are axo-dendritic or axo-somatic, but a range of other possible interneuronal contacts may be made. A single multipolar neuron may receive many thousands of synaptic inputs.

The smaller neuroglial cells produce structural and functional support to the neuroaxonal units, and are the predominant population in CNS tissue. The largest glial cells are the astrocytes that have numerous processes containing glial fibrils. The length and degree of branching of these processes is greater for the fibrous astrocytes of the white matter, than for the protoplasmic astrocytes of the gray matter. Adjacent astrocytes are linked to each other by gap junctions, and astrocyte processes terminate in end feet that are in close association with vascular endothelium and may induce the formation of inter-endothelial tight junctions, forming the basis of the ‘blood-brain-barrier’ (Couraud 1998). Astrocytes have a range of functions including provision of structural support and insulation for synapses, acting as an energy (glucose) source and acting to inhibit synaptic activity by taking up neurotransmitters. Astrocytes may be induced to express MHC class II and other co-stimulatory molecules (B7 and CD40) and are capable of antigen presentation to T lymphocytes in vitro (Dong and Benveniste 2001). Astrocytes may also have a role in down-regulation of CNS immune responses.

By contrast, oligodendrocytes are less branched cells that do not have gap junctions. White matter oligodendrocytes form the multilayered myelin sheath that surrounds and insulates the axon, and one oligodendrocyte may provide myelination for multiple axons (Baumann and Pham-Dinh, 2001). There are areas of unmyelinated axon (nodes of Ranvier) that form at the junction of myelin sheath produced by adjacent oligodendrocytes (internodes). The electrical insulation provided by myelin means that action potentials ‘jump’ between nodes which increases the speed of signal conduction relative to that which would occur in an unmyelinated axon. The function of gray matter oligodendrocytes is not defined, but they are arranged as ‘satellite’ cells to neurons and may be involved in neuronal homeostasis.

Microglia are relatively small glial cells with more sparse distribution in the neuropil. During CNS inflammation, microglia become phagocytic and capable of antigen presentation, and therefore act in similar fashion to infiltrating blood-derived macrophages to which they are likely related (Stoll and Jander 1999; Smith 2001). In demyelinating diseases these phagocytic cells accumulate intracellular lipid, appearing as ‘gitter cells’ with a foamy cytoplasm.

The ciliated ependymal cells form the lining to the ventricular spaces and modified ependyma line the choroid plexus and produce the cerebrospinal fluid (CSF) of the brain.