IN SPITE OF HETEROGENEITY, MS PROGRESSION REFLECTS SHARED CRITICAL MECHANISMS: NO

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Pathological studies of active multiple sclerosis lesions, derived from patients in the early (acute or relapsing) stage of the disease have revealed different patterns of demyelination, suggesting different mechanisms of immune mediated tissue injury. These different patterns of demyelination are only seen in classical active lesions, which are mainly seen in early disease stages, but are rare in patients with progressive MS. In the latter, ongoing demyelination and neurodegeneration is mainly reflected by the presence of slowly expanding lesions, slow expansion of cortical demyelination and diffuse white matter injury. Demyelination and neurodegeneration in the progressive stage is dominantly associated with oxidative injury, which can be driven by inflammation, microglia activation and oxidative burst and is amplified by chronic microglia activation, due to accumulation of lesion burden, by accumulation of mitochondrial injury and by iron accumulation due to aging and its liberation in actively demyelinating lesions. Thus, tissue injury in patients with progressive MS is only partly driven by inflammatory mechanisms, but is in part also accomplished by amplification factors related to brain aging and pre-existing brain damage. At very late stages of the disease, inflammation may decline to levels seen in age matched controls. However, age related neurodegeneration in these patients occurs on the background of a pre-damaged brain with exhausted functional reserve capacity. Oxidative injury as a major mechanism of tissue injury is also seen in a subset of patients in early disease stages, and these patients show a pattern of demyelination defined by pattern 3 or hypoxia-like tissue injury. It is likely, but so far not proven, that in these patients conversion into progressive disease may occur earlier in comparison to patients, showing other patterns of tissue injury. This view may be supported by the observation, that patients with neuromyelitis optica, who represent the prototype of patients with antibody mediated tissue injury in active lesions, in general to not convert into progressive disease. A similar situation may be seen in patients with inflammatory demyelinating MS like disease, who have high titers of circulating demyelinating anti-MOG autoantibodies. It is currently unclear, whether pathogenic auto-antibody responses exist in other patients with MS and whether such patients may have a different long term course in comparison to patients without pathogenic auto-antibodies.