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Neuronal and Axonal Damage in Early Multiple Sclerosis

B. Sultanov

Institute of Experimental Morphology and Anthropology, Bulgarian Academy of Sciences, Sofia

Multiple Sclerosis (MS) is considered to be the prototype of acquired primary demyelination. According to this concept neuronal and axonal pathology is not a dominating feature of early MS. However, recent imaging and morphological studies have challenged this historical view of preserved neuronal and axonal integrity during the early stages of MS. Early axonal damage has been demonstrated in vivo by proton magnetic resonance spectroscopy. Pathomorphological studies revealed axonal injury throughout active lesions (including acute lesions early within the course of the disease). Electronmicroscopic investigations on the central nervous system of Lewis rats with chronic relapsing experimental allergic encephalomyelitis (EAE), an animal model of MS, demonstrated axonal degeneration, preceeding demyelination, at the preclincal disease stage. Early neuronal dysfunction has been indicated by the findings concerning the regulation of gene expression in EAE. All these data are in favor of early neuron- and axon-protective therapies in MS.

Key words: multiple sclerosis, experimental allergic encephalomyelitis, neuron, axon.

Multiple sclerosis (MS) is considered to be the prototype of primary demyelinating central nervous system (CNS) disease with extensive myelin loss and relative preservation of axons [10]. Axonal injury is believed to occur as a consequence of demyelination, depending upon persistent disability and long-standing disease. Furthermore, a large variety of neuronal changes found in the brain and spinal cord lesions in MS patients were interpereted as secondary alterations like central chromatolysis and ischemic-anoxic neuronal damage [6].

Imaging and morphological studies of recent years have challenged this historical view of preserved neuronal and axonal integrity in MS. Several such investigations indicate that neuronal and axonal damage is a feature even of the first disease stages.

Magnetic resonance spectroscopy (MRS) is particularly useful for the study of axonal damage. Early axonal damage in patients with MS has been demonstrated in vivo by MRS, which shows decreased levels of the neuron-specific marker N-acetylaspartate (NAA) in active MS lesions [7]. De S t e f a n o et al. [4] performed proton MRS imaging in 88 patients with clinically definite MS. By assessing brain NAA in these patients with a wide range of disability and disease duration they showed that diffuse cerebral axonal damage begins in the early stages of MS, i.e. axonal injury and loss is not restricted to the end stages of the disease. Even complete clinical recovery from acute attacks in early MS does not mean that axonal damage has not occurred. Wallerian degeneration, mesured by the NAA concentration, at pons and cerebellar pe-

duncles was observed even in normal appearing white matter in the early stages of relapsing-remitting MS [2].

Direct evidence of axonal damage in MS has been provided by morphological studies. Charcot's [3] early description of the pathology of MS in 1868 included observations of axonal injury using the silver impregnation method. Recent investigations, applying modern morphological techniques, have provided further evidence for axonal damage in MS. Ferguson et al. [5] used beta-amyloid precursor protein as a histopatological marker of damaged axons and found evidence of axonal injury throughout active lesions and the margins of active chronic lesions in MS. Trapp et al. [11] used confocal microscopy and immunohistochemistry, applying an antibody to nonphosphorylated neurofilament epitopes, which are increased in demyelinating axons, for a three-diemensional reconstruction of terminal axonal ovoids. They demonstrated axonal transection throughout active lesions (including acute lesions early within the course of the disease) and within chronic active lesions, particularly at the edges of actively demyelinating lesions. The findings of the study by Trapp et al. further supported the notion, raised by Ferguson et al.,that axonal transections can begin very early in the disease process. Acute axonal damage, as defined by the accumulation of amyloid precursor protein, was found to occur not only in active demyelinating but also in remyelinating and inactive demyelinating lesions [1]. On the basis of their results Bitsch et al. [1] concluded that axonal injury is therefore, at least in part, independent of demyelinating activity, and its pathogenesis may be different from demyelination.

Recent evidence indicates early neuronal and axonal damage also in experimental allergic encephalomyelitis (EAE), an animal model of MS. Zaprianova et al. [15, 16] performed electronmicroscopic investigations on the brain and spinal cord of Lewis rats with chronic relapsing EAE (CREAE) at the preclinical stage and the first clinical episode of the disease. Their findings demonstrated axonal damage very early in the disease course. At the preclinical stage axonal degeneration was present, which preceeded the demyelination. During the first clinical episode of CREAE vesicular demyelination of the damaged axons occurred periaxonally. Nicot et al. [8] analysed the expression of genes encoding proteins that play critical roles in ions homeostasis, exocytosis, mitochondrial function and impulse conduction in the Lewis rat lumbar spinal cord during the clinical course of acute EAE. The results of their study concerning the regulation of gene expression in EAE indicate early neuronal dysfunction. These data are in full agreement with the suggestion of Zaprianova [13] in 1984 that the neuronal disturbance could have some as yet undemonstrated role in MS.

Another interesting finding concerning early neuronal damage in MS is the significant increase of GD1a, one of the major brain neuron ganglioside fraction, in the serum of patients with primary progressive MS and with relapsing-remitting MS during the first attack of the disease [14, 17].

The accumulating evidence demonstrating neuronal and axonal injury in early MS indicate that neurons are also targets of disease process in MS and that neuronal dysfunction may contribute to neurological abnormalities [12]. Future therapies, either separately or in combination with preexisting therapies, should target progressive pathological conditions either through direct intervention or through neuroprotective strategies [9].

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