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Review Articles

Current Knowledge of Multiple Sclerosis Pathogenesis

E. Zaprianova, D. Deleva, B. Sultanov, V. Kolyovska

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

The purpose of this review is to highlight the new concepts of the mechanisms of multiple sclerosis (MS) pathogenesis. For many years MS was considered to be primary demyelinating central nervous system (CNS) disorder with preserved neuronal and axonal integrity at the onset of the disease. However, in recent years several lines of evidence from imaging and morphological studies demonstrate that neuronal degeneration and axonal injury occur early in MS pathogenesis. Our electronmicroscopic investigations of CNS of Lewis rats with chronic relapsing experimental allergic encephalomyelitis, an animal model of MS, revealed at the preclinical disease stage an axonal injury which preceded the demyelination. At present, frequently multiple sclerosis is characterized as a neurodegenerative disease. This new concept of MS is in favour of early neuroprotective treatment strategies.

Key words: multiple sclerosis, experimental allergic encephalomyelitis, axonal injury, neuronal degeneration.

Introduction

One hundred and forty years have passed since in 1868 C h a r c o t [5] described the pathological and clinical features of multiple sclerosis (MS). Now, multiple sclerosis is recognized throughout the world, with around 2.5 million affected individuals. It affects twice as many women as it does men. The disease has an incidence of about seven per 100 000 every year and life time risk of one in 400 [7]. MS is the most common neurological disorders among young adults. However, in spite of the large amount of research undertaken, up to the present time the aethiology and the pathogenesis of MS remain unknown.

For many years multiple sclerosis was considered to be primarily a myelin sheath disorder with extensive myelin loss and relative preservation of neurons. Several concepts have been proposed regarding the pathogenetic factors responsible for the myelin sheath destruction. The most important still discussed in recent publications is autoimmunity [16, 26, 35, 37].

Multiple mechanisms of immune-mediated injury of myelin and oligodendrocytes have been postulated: cytokine-mediated injury of oligodendrocyte and myelin, digestion of surface myelin antigens by macrophages, including binding of antibodies against myelin and oligodendrocytes (i.e., antibody-dependent cytotoxicity), complement-mediated injury [25].

However, the concept of primary myelin and oligodendrocyte damage with axon sparing has been recently reconsidered with the demonstration that neuron-axonal lesions are an early phenomenon [19].

The classical view of MS as primary demyelinating central nervous system (CNS) disorder with preserved neuronal and axonal integrity at the onset of the disease has been challenged by imaging and morphological studies.

The application of modern magnetic resonance (MR) techniques has been extremely useful to start viewing MS as a diffuse CNS disease with an important neurodegenerative component [14]. MR spectroscopy (MRS) allows in vivo assessment of neuronal and axonal integrity based on the signal intensity of N-acetylaspartate (NAA), which is localized almost exclusively in neurons and axons in mature human brains [10, 24]. Spectroscopic studies have demonstrated that NAA values were abnormally low in the early stages of MS, even before significant disability was evident clinically. It was a strong relation between changes of NAA and clinical disability both in acute and chronic MS [10, 20, 21]. B l a m i r e et al. [2] used MRS to investigate the degree of neuronal damage in the cervical spinal cord in MS and found that NAA was reduced by 32% in MS patients relative to controls, indicating significant neuronal damage. C i f e l l i et al. [4] performed MR imaging and MRS studies to estimate thalamic neuronal loss in MS patients. Their results indicate that neuronal loss in MS can be substantial (30-35% reduction).

Death of neurons has been documented in greater detail in experimental allergic encephalomyelitis (EAE), an animal model of MS. One quarter of spinal cord ventral horn neurons are lost in Lewis rats with EAE induced with myelin basic protein (MBP) [29] and neuronal apoptosis occurs in the CNS of mice and rats with MBP — or myelin oligodendrocyte glycoprotein peptide (MOG) — induced EAE [11, 15, 23]. H o b o m et al. [15] analyzed the mechanisms and kinetics of neuronal death in EAE by communing an electrophysiological in vivo assessment of the optic pathway with the investigation of retinal ganglion cell counts. They found that neuronal cell death together with decreased visual activity values occurred before the onset of clinical symptoms.

However, MR techniques are not able to differentiate between acute and long-standing axonal damage. They can only reflect the accumulation of axonal damage dysfunction. In contrast, histopathological investigations are able to distinguish between acute axonal damage and permanent loss of axon. The latter can be measured by the number of axon counted after Bielschowsky's stain or immunohistochemical neurofilament staining. Acute axonal damage can be detected by immunohistochemistry for the amyloid precursor protein (APP) [27] which is produced in neurons and accumulates at sites of recent axon transection or damage. It persists in transected axons for a period of < 30 days. In histopathological studies, a significant reduction of axon density was found in MS lesions [8, 22]. De L u c a et al. [8] estimated the axon density in the corticospinal tracts from the medulla to the lumbar spinal cord in post-mortem material of 55 MS patients and 33 matched controls. Their results indicated a significant reduction of axon density at all levels investigated in MS cases when compared with controls.

F e r g u s o n et al. [13] used APP and found evidence of axonal injury throughout active lesions and the margins of active chronic lesions in MS. T r a p p et al. [33] used confocal microscopy and immunohistochemistry, applying an antibody to nonphosphorylated neurofilament epitopes, which are increased in demyelinating axons, for a three-dimensional reconstruction of terminal axonal ovoids. They demonstrated axonal transec-

tion 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. K o r n e k et al. [17] quantified acute axonal injury, defined by immunoreactivity for APP in dystrophic neuritis in the CNS of 22 MS patients and 18 rats with chronic EAE, induced with MOG. The highest incidence of acute axonal injury was found during active demyelination, which was associated with axonal damage in periplaque and in normal appearing white matter of actively demyelinating cases. In addition, low but significant axonal injury was also observed in inactive demyelinating plaques. In contrast, no significant axonal damage was found in remyelinated shadow plaques. The data of K u h l m a n n et al. [18] confirm these investigations. Most APP-positive axons were detected within the first year after disease onset. The numbers of APP-positive axons in MS lesions correlated with the disease duration and course.

As it was mentioned above, several lines of evidence demonstrate that axonal injury, considered at one time to be a late phenomenon is now recognized to occur early in MS pathogenesis. However, the relative roles of demyelination and axonal loss have not been fully clarified, nor have their possible interrelationships been elucidated. In the study of B i t s c h et al. [1] axon reduction and signs of acute axonal damage were quantified in early lesion development of chronic MS and correlated with demyelinating activity and inflammation. On the basis of data obtained, they concluded that axonal injury is therefore, at least in part, independent of demyelinating activity and its pathogenesis may be different from demyelination. R a m m o h a n [28] suggested that although generally considered to be sequelae of demyelination, it is possible that axonal injury in MS is indeed a primary event. D e L u c a et al. [9] found that there was little correlation between plaque load and axonal loss in post-mortem material from the cerebrum, brain stem and spinal cord of 55 MS patients with an age of 25—83 years and length of disease history ranging from 2 to 43 years. Therefore, they think that the possibility that demyelination is not the primary determinant warrants consideration.

For the first time, our electronmicroscopic investigations demonstrated in the spinal cord of Lewis rats with chronic relapsing EAE (CREAE) at the preclinical stage of the disease very early axonal injury which preceded the destruction of myelin sheath. CREAE was induced by inoculation with highly purified quinea-pig myelin and complete Freund's adjuvant, followed by treatment with low dose cyclosporine A. During the first clinical episode of CREAE demyelination of the damaged axons occurred periaxonally [31, 32, 40, 41].

In recent years it has become increasingly evident that axonal degeneration is primarily responsible for permanent neurological deficit. The pathophysiology of axonal injury remains till now speculative. Several mechanisms lead to axonal loss, including inflammatory secretions, loss of myelin-derived support, disruption of axonal ion concentrations, energy failure and Ca ions accumulation [12]. Suspicion is growing that sodium channels may also contribute to the axonal degeneration [3, 30, 36].

The role of neurons in MS pathogenesis has been suggested for the first time in 1984 by Z a p r i a n o v a [39]. Axonal injury and neuronal loss are now recognized to be hallmarks of MS in addition to neuroinflammation and demyelination [38]. According to C h a u d h u r i and B e h a n [6] multiple sclerosis is not autoimmune disease but a genetically determined disorder characterized by metabolically dependent neurodegeneration. T r a p p [34] characterized multiple sclerosis as chronic disabiliting neurodegenerative disease.

The new concept of multiple sclerosis as an neurodegenerative disease has important clinical implications. Specific treatment strategies need to be developed that act within the CNS to prevent neurodegeneration and need to be provided from the earliest stages of disease [42].

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