NEUROPROTECTION AND GLATIRAMER ACETATE: THE POSSIBLE ROLE IN THE TREATMENT OF MULTIPLE SCLEROSIS

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1. INTRODUCTION

Multiple Sclerosis (MS) is the most common inflammatory demyelinating disease of the central nervous system (CNS). It is believed to be an immune-mediated disorder in which the myelin sheath or the oligodendrocyte is targeted by the immune system in genetically susceptible people. Oligodendrocytes synthesize and maintain the axonal myelin sheath of up to 40 neighbouring nerve axons in the CNS. Compact myelin consists of a condensed membrane, spiralled around axons to form the insulating segmented sheath needed for saltatory axonal conduction: voltage-gated sodium channels cluster at the unmyelinated nodes of Ranvier, between myelin segments, from where the action potential is propagated and spreads down the myelinated nerve segment to trigger another action potential at the next node.

The pathological hallmark of MS is the demyelinating plaque which consists of infiltrating T lymphocytes and macrophages, damage to the blood-brain barrier and loss of myelin. The composition of the inflammatory infiltrate varies depending on the stage of demyelinating activity. Early symptoms of MS are widely believed to result from this inflammatory axonal demyelination which leads to slowing or blockade of axonal conduction. The regression of symptoms has been attributed to the resolution of inflammatory edema and to partial remyelination.

Although MS is primarily an inflammatory autoimmune disease, it has become evident that axonal loss plays an important role in the pathogenesis of disability for patients with MS[1]. While axonal pathology was elegantly and precisely described in classic MS neuropathology studies more than a century ago[2,3], it has only recently reemerged as a major focus of research[4]. The central question to be addressed is not whether there is axonal loss in MS but when and to what extent does the axonal loss occur. The timing and degree of axonal loss is of importance not only in its relationship to the aetiology of the disease but may well be central to the appearance of clinical symptoms and the progressive

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deterioration associated with the disease. The fact that axonal loss is irreversible has important implications for when, and what therapeutic intervention should be used.

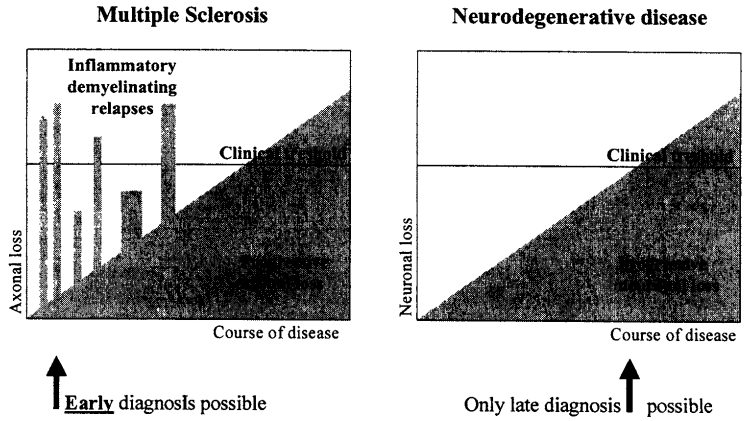

Figure 1: Early diagnosis and therapy of the demyelinating neurodegenerative disorder MS is possible in comparison to other neurodegenerative diseases like M. Parkinson or Alzheimer

It is likely that various mechanisms contribute to axonal damage during different stages of disease. In active lesions, the extent of axonal transsection correlates with inflammatory activity while even there seems to be an inflammation-independent axonal loss[5]. Hence, axonal loss may be caused by inflammatory products of activated immune and glial cells, including proteolytic enzymes, cytokines, oxidative products and free radicals, although the precise molecular mechanisms of axonal damage are poorly understood. In addition the magnitude of axonal loss in chronic MS lesions without pronounced inflammatory infiltrates suggests that mechanisms other than inflammatory demyelination contribute to the degeneration of axons. Several conditions interfere with attemps of axonal regrowth after lesions develop. These include the lack of neurotrophic factors that support growth, the presence of a glial scar (depending on the site of lesion) or the presence of inhibitory molecules that impede axonal growth. Recent evidence shows that axon degeneration following injury has similarities with the cellular mechanisms underlying programmed cell death[5].

The concept of MS as an inflammatory neurodegenerative disease highlights the importance of an active therapeutic approach. But since lesions outnumber clinical relapses by much as 10:1 and, in addition, inflammation-independent axonal degeneration may occur and add to the considerable continuing subclinical pathophysiological process, tissue

damage even in the absence of clinical manifestations may take place. Because MS has its characteristic clinical phenotype with clinical relapses and remissions, MS could be diagnosed and treated at an earlier timepoint of the disease in contrast to other neurodegenerative disorders like M. Parkinson or M. Alzheimer (Figure 1). Theoretically, an antiinflammatory and neuroprotective treatment could be started early in MS before most axons and neurons would be lost.

The early and continuous application of disease-modifying therapies offers the possibility that accumulating axonal degeneration and permanent functional disability can be prevented or delayed. The clinical challenge in this respect is therefore the early decision for an individual MS patient on anti-inflammatory and neuroprotective MS therapy.

2. DETECTING AXONAL DAMAGE IN MS

It is well known that there is axonal loss within chronic MS lesions. The use of immunocytochemical methods that stain axonal end-bulbs demonstrates evidence of axonal injury even in acute and early lesions[4]. Axonal injury in MS lesions will lead to both Wallerian degeneration of the axon and also retrograde degeneration of the cell body. The functional consequences of the axon injury will depend on the numbers of injured axons and the topographical organization of the fibres coursing through the lesion[5].

Besides neuropathology, the other technical advance that has drawn attention to axonal loss in MS is the use of magnetic resonance imaging (MRI) and spectroscopy (MRS)[6]. The use of these techniques is helpful in characterizing the underlying pathologic processes in multiple sclerosis. There is consensus that T2-weighted MRI reflects the broad spectrum of pathological changes, including inflammation, edema, demyelination, gliosis and axonal loss. Changes in the number and volume of lesions on T2-weighted MRI (lesion load) are sensitive but nonspecific indicators of disease activity and the response to treatment. There is evidence that – below the detection treshold - the normal-appearing white matter is not normal at all in patients with MS.

Besides inflammatory markers, techniques to quantify images from MRI have revealed significant tissue atrophy in the spinal cord and brain in MS patients. These measures of whole tissue cross-sections or volume do not, however, discriminate between myelin and axonal loss. A powerful technique for the analysis of the biochemical components of tissue in life is magnetic resonance spectroscopy (MRS). The normal proton spectrum in brain tissue is dominated by a signal from N-acetyl aspartate (NAA), an amino acid that appears to be specifically localized to neuronal cell bodies and axons[7]. There are a number of studies demonstrating that the amount of NAA is decreased in MS lesions but importantly also in apparently normal white matter[8,9].

Hypointense lesions on enhanced T1-weighted images ("T1 black holes") have been reported to correspond to areas where chronic severe tissue disruption has occurred[10]. When one considers the evolution of a MS lesion, the T1 black hole usually represents the end stage of the process, when significant demyelination, axonal loss, and reactive gliosis have occurred. The degree of hypointensity appears to correlate with a decrease in the magnetization transfer ratio (MTR) and with axonal loss as quantified by a reduction in the NAA peak on MR spectroscopy or in histopathology[11,12] (Figure 2). This measure is beginning to show a better correlation with disease progression than either T2 disease burden or Gadolinium (Gd)-enhancing lesions in patients with secondary progressive MS. At the time of Gd-enhancement, a significant proportion of lesions will demonstrate some

hypointensity on T1-weighted images. Over a period of time, most enhancing lesions become isointense to white matter and their MTR returns to that of normal-appearing white matter. A proportion of Gd-enhancing lesions will remain hypointense and eventually become T1 black holes.

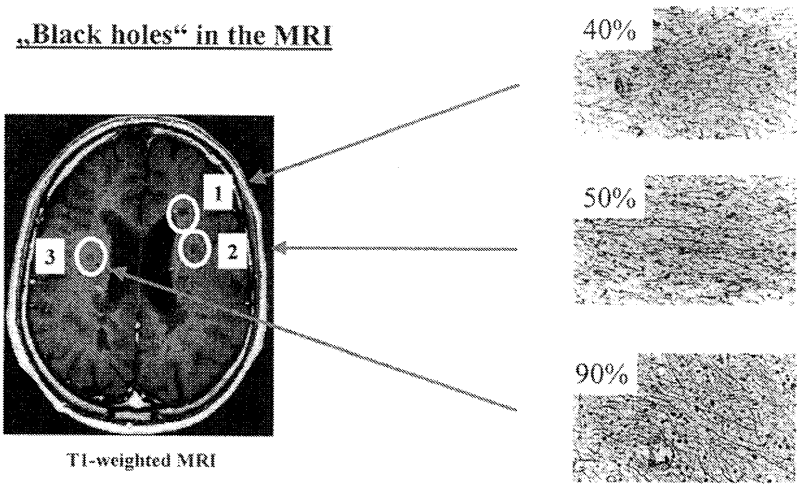

Figure 2: T1 hypointense lesions (black holes) are strongly associated with axonal density, emphasizing their role in monitoring progression in multiple sclerosis.

Roughly 30% to 40% of new lesions will evolve into persistent black holes over short time periods (5 to 12 months) and represent severe and irreversible tissue disruption. Evidence from a large number of postmortem and in vivo MRI studies have substantiated that permanent T1 hypointensive lesions correspond to areas of severe axonal damage and myelin loss. Consistent with these findings, data also indicate that the overall extent of hypointense brain lesions correlates with the degree of MS-related disability[12].

3. NEUROTROPHIC FACTORS AS SPECIAL NEUROTROPHIC AGENTS

Damaged neurons in the CNS attempt to repair themselves although these attemps are usually not succesful. An important component of restoration of function expecially in a disorder like MS in which axons are damaged, must include the potential of axonal repair. One of the more promising approaches to encourage axonal growth is the administration of growth-supporting molecules, particulary specific growth factors.

Historically, nerve growth factor (NGF) was first and for a long time, the only known neurotrophic factor which was primarily best characterized by its anti-apoptotic function on

neurons during development. Following the discovery of structurally related proteins with a similar neurotrophic function, the term "neurotrophin" was introduced for this protein family of homodimers with a conserved region containing a cystein bond in the core of the molecule and with duplicate sites for receptor binding[13].

The neurotrophins of the NGF family are not the only proteins with neurotrophic function (Table 1). In recent years, two additional families of protein growth factors have been characterized, which exert strong neurotrophic activity on developing neurons. The first one is the family of the glial-cell-derived neurotrophic factor (GDNF) ligands (GFLs) including GDNF and three related proteins[14]. The second family is formed by the neuropoietic cytokines, which besides other more pleiotropic cytokines includes ciliary neurotrophic factor (CNTF) and leukemia inhibitory factor (LIF)[15]. Although structurally different, these three families are now collectively referred to as neurotrophic factors. In addition, neutroprotective activity has been reported for growth factors not belonging to any of the three neurotrophic factor families, one prominent example beeing insulin-like growth factor (IGF)-1[16].

Table 1: Different protein families with neurotrophic function

NGF-related neurotrophins	Nerve growth factor (NGF)
	Brain-derived neurotrophic factor (BDNF)
	Neurotrophin (NT)-3
	Neurotrophin (NT)-4/5
GDNF family ligands	Glial-cell-derived neurotrophic factor (GDNF)
	Neurturin
	Artemin
	Persephin
Neuropoetic cytokines	Ciliary neurotrophic factor (CNTF)
	Leukemia inhibitory factor (LIF)
Miscellaneous factors	Insulin-like growth factor (IGF)-1
	Neuregulins (GGF-2)

In a therapeutical context it is important to note that the functions of neurotrophic factors are not restricted to neural development. It is evident that neurotrophins act on mature neurons, most prominently on injured and degenerating nerve cells[17,18]. Neurotrophic factors can protect and rescue neurons in a large number of experimental models. Of particular relevance to MS is the demonstrated ability of BDNF and NT-3 to promote regeneration of long tracts in the spinal cord[19]. In addition, the expression levels of neurotrophins and their receptors are strongly regulated in pathological conditions, thus

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