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Neuronal Degeneration at the Earliest Stages of Multiple Sclerosis

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In recent years, has become more evident that neuronal damage is an early pathological sign in multiple sclerosis (MS). In our study, we analysed cervical spinal cord specimens from MS patients, died accidentally during the first five years of disease duration. A severe degeneration of anterior horn neurons was detected in the specimens from two patients suffered of MS only one year. This finding reveals for the first time neuronal injury very early in MS pathogenesis. It further support the concept of multiple sclerosis as a neurodegenerative disorder. The data of the present investigation argue once again for the early neuroprotective treatment of MS patients.

Key words: multiple sclerosis, cervical spinal cord, neuron, degeneration.

Introduction

Multiple sclerosis (MS) is considered to be prototype of acquired primary demyelinating disease in the central nervous system (CNS) with extensive myelin loss and relative preservation of neurons [10]. According to this concept neuronal and axonal injury is not a dominating feature of early MS and is believed to occur as a consequence of demyelination. However, recent imaging and morphological studies has challenged this historical view of preserved neuronal and axonal integrity at the earliest clinical stages of MS [11]. Proton magnetic resonance (MR) spectroscopy by monitoring levels of N-acetylaspartate, a putative marker of axonal integrity, has been particularly illuminating by showing indirect evidence of neurodegeneration in both lesional and non-lesional brain tissues from the earliest stages of MS [3]. F i l l i p p i et al. [4] used MR imaging and spectroscopy to study abnormalities in the brain of patients with MS. They concluded that axonal and neuronal injury occurs early in the course of MS, leading to widespread damage even before the disease is diagnosed clinically. K u h l m a n n et al. [6] investigated the occurrence of acute axonal damage determined by immunocytochemistry for amyloid precursor protein (APP) which is produced in neurons and accumulates at sites of recent axon damage. Most APP-positive axons were detected within the first year after disease onset. In previous electronmicroscopic studies of ours we observed axonal degeneration which preceded demyelination in the spinal cord of Lewis rats before the onset of clinical symptoms of chronic relapsing experimental allergic encephalomyelitis (CREAE), an animal model

of MS [15]. Neuronal death also in the preclinical stage of EAE was reported by H o b o m et al. [5]. However, there are no data illustrating directly neuronal injury in early MS. Therefore, the aim of the present study was to look for neuronal changes during the early stages of MS analysing cervical spinal cord sections from clinically defined MS patients, died accidentally during the first five years of the disease.

Materials and Methods

Cervical spinal cord sections from 9 multiple sclerosis cases and from 5 control cases were used in this study from the large pathomorphological collection in the Department of Neuropathology at the Institute of Psychiatry and Neurology in Budapest, Hungary. All MS cases were patients with clinically defined MS [according to 9]. Three of them suffered of early MS (course of the disease of one year) and five of them have MS for 3-5 years. Causes of death included myocardial infarction (seven cases) and suicide (two cases). The controls were patients who died of nonneurological diseases and without pathological changes within CNS.

Sections were stained using routine neuropathological staining for neurons, glia and myelin (Nissl staining and luxol fast blue staining).

Results

Severe degeneration of motoneurons in the anterior horn, demonstrated by Nissl staining, was detected in the sections of the cervical spinal cord of two patients suffered of MS with only one year course of the disease (cause of death — suicide) (Fig. 1 and Fig. 2). Demy-

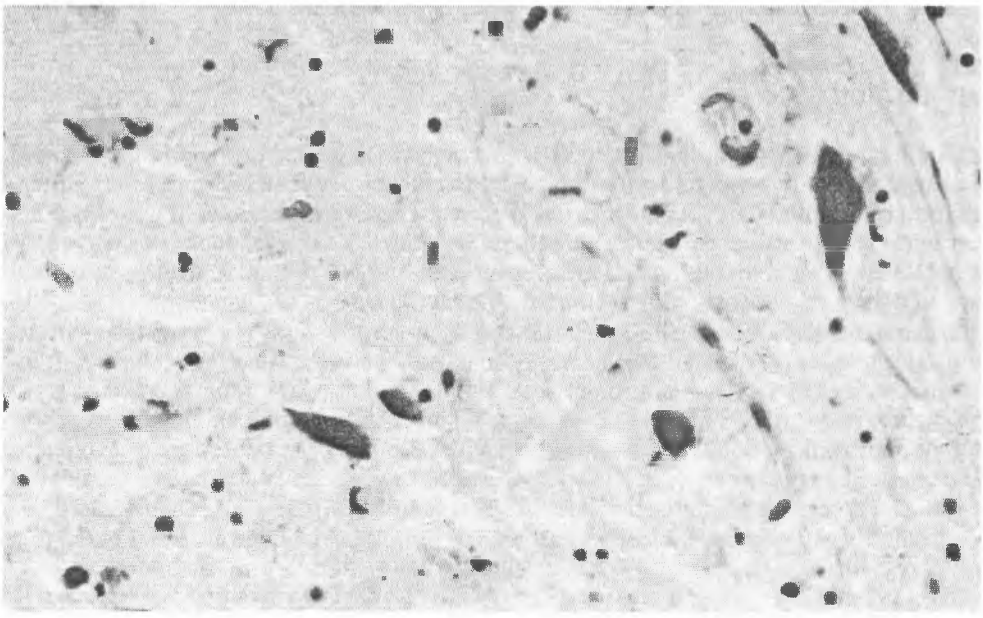

Fig.1. Degenerated motoneurons in the anterior horn of the cervical spinal cord of a patient with early MS (one year course). Nissl staining (× 250)

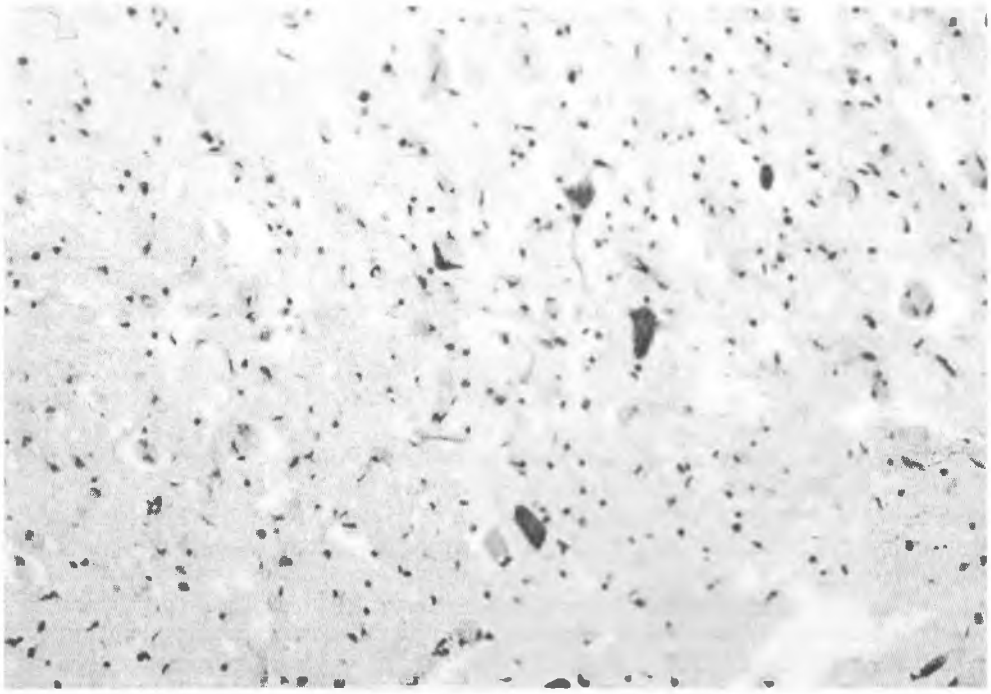

Fig. 2. Severe destruction of anterior horn neurons of the cervical spinal cord of another patient with early MS (one year course). Nissl staining (× 200)

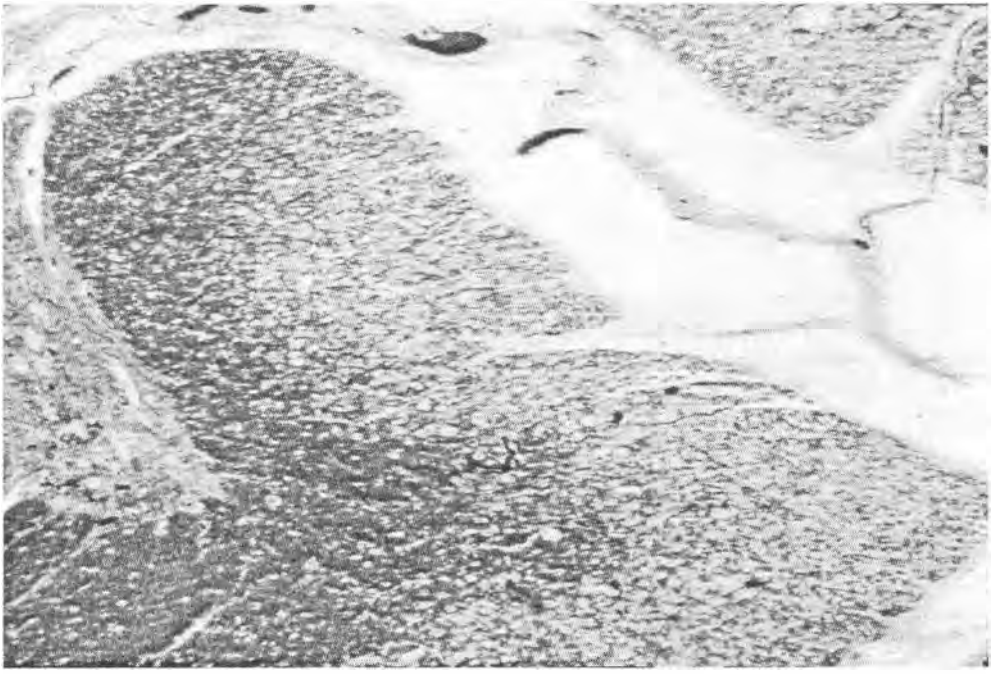

Fig. 3. Demyelination of lateral pyramidal tract in the cervical spinal cord of a patient with early MS (one year course). Pallor of the pyramidal tract. Luxol fast blue staining (× 100)

elination of lateral pyramidal tract in cervical spinal cord was present, detected by the pallor of the tract after luxol fast blue staining (Fig. 3).

Degenerated anterior horn neurons were not found in the sections of the cervical spinal cord of others MS cases and of controls.

Discussion

The analysis of specimens from patients dying accidentally at earliest stages of MS (one year duration of the disease) revealed neuronal degeneration of anterior horn neurons in the cervical spinal cord. The cervical spinal cord has been chosen for the analysis of neuronal changes in early MS for two reasons:

a) multiple sclerosis in the spinal cord is a common presentation of the disease. Involvement of the long tracts leads to muscular weakness, sensory loss or paraesthesiae and bladder disturbances;

b) the cervical part is the most common site for MS plaques in the spinal cord [1]. Neuronal degeneration so early in MS pathogenesis was not described. Our findings are in accordance with the observations of L a s s m a n n [7] concerning the lesions in CREAE. He found in one animal in addition of demyelinating plaques an extensive anterior horn neuron destruction.

As it was mentioned above, neuronal cell death was detected to occur even before the onset of clinical symptoms of EAE [5]. The authors analysed the mechanism and kinetics of retinal ganglion cell (RGC) apoptosis by combining an electrophysiological in vivo assessment of the optic pathway with the investigation of RGC counts. They found that RGC death together with decreased visual acuity values was present before the appearance of clinical symptoms of EAE. N i c o t et al. [8] investigated 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.

In our previous study an increase of GD1a ganglioside, one of the major human brain neuronal ganglioside fraction, was observed in the serum of patients with MS during their first attacks of the disease [14]. It was suggested that this increase is connected with the neuronal damage in early phases of MS pathogenesis.

Our findings and the data of the others authors cited above provide evidence of early neuronal injury in MS and EAE. They further support the concept of multiple sclerosis as a neuronal ganglioside ganglioside disease [12]. For the first time Z a p r i a n o v a [13] suggested that the neuronal disturbance could have some as yet undemonstrated role in MS. C h a u d h u r i and B e h a n [2] proposed that MS is not an autoimmune disease but a genetically determined disorder characterized by metabolically dependent neurodegeneration.

In conclusion, the present study reveals for the first time a severe degeneration of anterior horn neurons in cervical spinal cord of MS patients, died accidentally during the first year of the disease. The detection of neuronal injury at the earliest stages of MS argue once again for the early treatment of MS patients with agents directed towards neuronal protection.

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