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COGNITIVE IMPAIRMENT IN PATIENTS WITH MULTIPLE SCLEROSIS : LITERATURE REVIEW

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S u m m a r y. Multiple sclerosis (MS) is most common immune-mediated inflammatory demyelinating disease of the central nervous system, which often causes progressive neurological disability. The paper reviews scientific reports on multiple sclerosis (MS) concerning cognitive impairment. Many patients with MS have or will develop some cognitive deficits. Progressive symptoms affect not only motor skills but also worsen activities of daily living and reduce independence. This part of MS clinical picture is better known due to neuropsychological research and neuroimaging. Cognitive behavioral therapy and education programs are promising psychosocial interventions to improve coping and lessen cognitive impairment.

K e y w o r d s: multiple sclerosis, cognitive impairment, cognition, neuropsychology

INTRODUCTION

Multiple sclerosis (MS) is most common immune-mediated inflammatory demyelinating disease of the central nervous system (CNS). It is also regarded as the most common neurological disease affecting young adults. Twice as many women are affected as men, except for primary-progressive MS, where males and females are affected almost equally [12]. MS attacks the myelinated axons in the CNS destroying the myelin and the axons to varying degrees [6]. MS cause is unknown, but it appears to involve a combination of genetic susceptibility and a nongenetic trigger, such as a virus, metabolism, or environmental factors, that together result in a self-sustaining autoimmune disorder that leads to recurrent immune attacks on the CNS. In 2015, about 2.3 million people were affected globally with rates varying widely in different regions and among different populations [4]. The course of MS is highly varied and unpredictable. In most patients, the disease is characterized initially by episodes of reversible neurological deficits which is often followed by progressive neurological deterioration over time [6].

MATERIALS, METHODS AND AIM OF THE STUDY

The present article reviews scientific reports on multiple sclerosis concerning cognitive impairment. The aim of the study is to present the diversity of cognitive impairment in patients with MS and to describe its impact on the disease progress.

RESULTS

Multiple sclerosis

The core of MS phenotypes is a series of relapsing and progressive episodes [11]. The pattern and course of MS is further categorized into several clinical subtypes, i.e. relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS) and progressive-relapsing MS (PRMS). These

phenotypes are modified by the assessments of disease activity and progression. Disease activity is determined by clinical relapses or MRI evidence as contrast-enhancing lesions and/or new or unequivocally enlarged T2 lesions. Disease progression is a process that is independently quantified from relapses, and is characteristic of primary and secondary progressive MS.

Relapsing–remitting MS is the most common form, affecting about 85% of MS patients. It is characterized by flare-ups (relapses or exacerbations) of symptoms followed by periods of remission, when symptoms improve or disappear. Secondary progressive MS may develop in some patients with relapsing–remitting disease [10]. Symptoms of MS could be manifested as blurred or double vision, which is sometimes an early symptom of MS, clumsiness or lack of coordination, loss of balance, numbness, tingling, weakness in the arm or leg and cognitive impairment. In many cases treatment with disease-modifying agents helps delay symptom progression. The disease course continues to worsen with or without periods of remission or leveling off the severity of symptoms (plateaus). Primary progressive MS affects approximately 10% of MS patients. Symptoms continue to worsen gradually with time. There are no relapses or remissions, but there may be occasional plateaus. This form of MS is more resistant to drugs typically used to treat the disease. Progressive-relapsing MS is a rare form, affecting fewer than 5% of patients. It is progressive from the onset, with intermittent flare-ups of worsening symptoms along the way. There are no periods of remission [6].

The disease is diagnosed on the basis of clinical findings and supporting evidence from ancillary tests, such as magnetic resonance imaging (MRI) of the brain and examination of the cerebrospinal fluid (CSF). MS typically occurs in adults aged 20 to 45 years. Occasionally, it presents in childhood or late middle age [6]. MS with the onset after 40 years is progressive in over 60 % of patients.

A variety of factors have been identified as possible prognostic markers of MS that may modify the disease course or predict exacerbations. However, none is an established and reliable, and chances to accurately predict the outcome for individual patients with MS are quite limited [16]. The relapsing form of MS is generally associated with a better prognosis than progressive disease [17].

Cognitive impairment

Cognitive impairment is a common and debilitating feature of MS that has only recently gained considerable attention. Clinical neuropsychological studies have made apparent the multifaceted nature of cognitive impairment in MS, and continue to broaden our understanding of its complexity [3]. Although being long considered as pure white matter (WM) disease, growing evidence indicates the gray matter (GM) is affected in MS as well, and that GM pathology correlates with cognitive functions deterioration in MS. Indeed, MS is increasingly recognized to cause cognitive deficits from its early stages [5].

The most recent research suggests that cognitive impairment correlates with brain lesions and brain atrophy. The examination of cognitive impairment is usually based on particular neuropsychological batteries. However, it can be insufficient to come out with precise diagnosis. Currently most promising methods consist of neuroimaging markers, such as diffusion tensor imaging, magnetization transfer ratio, and N-acetyl aspartate [13].

Conducted research shows that up to 65 % of MS patients have cognitive deficits such as episodic memory, sustained attention, reduced verbal fluency [8]. Previous epidemiological studies also reported 40-70% frequency of cognitive impairment in patients with MS [2, 14]. However, cognitive MS domain is information processing speed. It is the first syndrome of cognitive dysfunction, and most frequently affected in MS. Occasionally, these impairments occur even before the appearance of physical symptoms. [13].

Cognitive and neuropsychiatric disorders in patients with MS have been widely investigated. Studies of the profile and prevalence of such disorders mostly come from North America and Western Europe, but lately a few studies have appeared in Latin America (LATAM) reporting results specific to the region [18]. Multicentre studies carried out by Vanotti *et al*. in Latin America have shown that 43% of the patients have cognitive impairment and 34.5% in early stages of the disease, 29% depression and 20.9% neuropsychiatric disorders. The profile of cognitive impairment corresponds to alterations in visual and verbal memory, attention, information processing speed, and in verbal fluency. The neuropsychiatric profile showed disorders manifested in anxiety, depression, apathy and

irritability domains. Several tests are used to evaluate MS, e.g. Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ), Brief Repeatable Battery of Neuropsychological Tests (BRB-N) and Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), Paced Auditory Serial Addition Test (PASAT), and Symbol Digit Modalities Test (SDMT).

Huijbregts *et al.* present results of two studies conducted to investigate cognition in different MS subtypes. First was a cross-sectional study carried out among 108 patients with relapsing–remitting (RR) MS, 71 patients with secondary progressive (SP), 55 with primary progressive (PP), and 67 healthy controls. The second study involved a follow-up assessment after 2 years, and included 30 SPMS patients, 25 PPMS patients, and 33 controls. Brief Repeatable Battery of Neuropsychological Tests (BRB-N) was used in all cognitive assessments. All patient groups demonstrated cognitive deficits compared to healthy controls. RRMS patients were less affected compared to patients with progressive MS subtypes on PASAT and SDMT. These differences were attenuated after control test for physical disability level as measured by Expanded Disability Status Scale. RRMS and SPMS patients were more severely impaired than PPMS patients on 10/36 Spatial Recall Task and Word List Generation. Results of the follow-up study indicated that both progressive MS subtypes showed lack of improvement compared to controls on PASAT and SDMT but not in other tasks tested by BRB-N, which indicated that performance of tasks requiring multiple abilities concurrently, i.e. visuo-spatial ability and processing speed (SDMT) or working memory and processing speed (PASAT) is most likely to decline over time [7].

Benešová *et al.* designed an observational, multicentre, prospective, single-arm, phase IV study carried out in 13 MS centers in the Czech Republic. They wanted to evaluate changes in cognition, fatigue, and disability status in 300 patients suffering from RRMS, treated with subcutaneous (sc) interferon (IFN) β-1a over 2 years. Cognition status was assessed using PASAT, fatigue by Fatigue Descriptive Scale (FDS), and disability using Expanded Disability Status Scale (EDSS), at baseline, and after 6, 12 and 24 months. The proportion of patients with cognitive improvement was higher compared with those with a stable or decreased PASAT scores at all time points, and the average cognitive performance improved during follow-up period. Also the proportion of patients with stable or improved fatigue and EDSS scores was higher compared with those in which FDS or EDSS scores declined; this was found at all time points of the examined group. The results have demonstrated a stable or improved cognitive performance, fatigue status, and disability level in majority of RRMS patients treated with sc IFN β-1a over a two-year follow-up period [1].

Jongen *et al.* describe cognitive impairment in MS like typically involving complex attention, information processing speed, (episodic) memory and executive functions. Dysfunction in free recall from long-term memory, working memory, and abstract reasoning is frequently observed [8, 15]. This is observed in the subclinical radiologically isolated syndrome, clinically isolated syndrome, and all phases of clinical MS [8]. Rogers *et al.* add that these phenomena can be a major source of vocational disability, social impairment, and impoverished quality of life. In pediatric-onset MS cognition is frequently impaired and worsens relatively rapidly. Depression, anxiety and fatigue aggravate the symptoms [15]. Despite weak correlation with disease duration and physical disability status, the degree of cognitive impairment in MS has been related to the extent of topographically specific neuronal tissue damage and loss. Additional clinical factors including disease course, fatigue, affective disturbance, and medication can affect the degree of MS-related cognitive impairment [15].

Furthermore, the identification of a biomarker with good diagnostic and prognostic potential is of great importance for monitoring and preventing cognitive impairment in MS patients. Gentile *et al*. indicate that a possibility arises from the combination of two different measures of neuronal injury, i.e. the levels of amyloid-β(1-42) in the CSF which were found to be associated with cognitive decline in Alzheimer disease (AD), and the brain synaptic plasticity which is a measure of cognitive reserve and can be explored by means of transcranial magnetic stimulation. The link between amyloid-β(1-42) and long-term potentiation (LTP) is discussed [5].

Diagnostic problems are strictly connected with treatment procedures. There are two main cognitive therapies: pharmacological by disease modifying drugs (DMD), symptomatic treatment, and non-pharmacological interventions

that focus on psychological and physical rehabilitation. In relapsing-remitting MS timely and adequate disease modifying drug treatment may stabilize or possibly improve cognition [8]. It requires further studies in order to establish the role of medication in cognitive disorders in patients with MS. Cognitive behavioral therapy and education programs are promising psychosocial interventions to improve coping and lessen cognitive symptoms [8]. Some trials have shown positive association between physical activity and cognitive functions [8, 13].

DISCUSSION

The frequency of cognitive impairment such as episodic memory, sustained attention and reduced verbal fluency in patients with MS was notable. The neuropsychiatric profiles of patients with SM show disorders like anxiety, depression, apathy and irritability.

Depression, anxiety and fatigue could aggravate cognitive impairment [15]. Relapsing–remitting MS is the most common form affecting MS patients. Huijbregts SC. *et al.* conclude that RRMS patients were less affected compared to patients with progressive MS subtypes [7]. A study showed that 53% of the patients with NEDA3 had cognitive impairment. This finding highlights the need for taking cognitive assessment into account when determining therapeutic efficacy [18].

Cognitive impairment is correlated with brain lesions and atrophy. This creates a demand to find markers that might be useful for identifying patients with risk of cognitive impairment at an early stage of the disease. Other adverse events also require further studies to fully elucidate the problem. Cognitive dysfunctions correlate with MRI brain lesions and regional atrophy, and increase in MRI abnormalities can predict further worsening. Experimental MRI indicates a crucial role for (focal) cortical lesions and atrophy, abnormal cortical integrity, and early changes in normal structure of the brain tissue. Functional MRI suggests compensatory reorganization and adaptation changes in neural activities [8].

Impaired cognitive functions affect financial situation of MS patients negatively and independently of physical disability. This warrants cognitive testing as a routine measure in health care services for MS patients [9].

CONCLUSIONS

MS is most common immune-mediated inflammatory demyelinating disease of the CNS, which often causes progressive neurological disability. In most patients, the disease is characterized initially by episodes of reversible neurological deficits, which is often followed by progressive neurological deterioration over time [6]. Symptoms of MS include blurred or double vision, clumsiness or a lack of coordination, loss of balance, numbness, tingling, weakness in the arm or leg and cognitive impairment. Patients with SM present diversity of cognitive impairment.

Cognitive behavioral therapy and education programs are promising psychosocial interventions in order to improve coping and lessen cognitive symptoms. Leisure activities enhance cognitive reserve [8]. Some trials have shown positive association between cognitive function and physical activity [13, 8]. But there is no evidence-based symptomatic drug treatment, nor are there optimal non-pharmacological approaches.

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