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COGNITIVE ASPECTS IN MULTIPLE SCLEROSIS

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SUMMARY

Background: *Cognitive dysfunction appears all through the course of multiple sclerosis (MS). Mild and moderate cognitive impairment is present in up to 40% of MS patients and severe cognitive decline affects more than 50% of patients in progressive course of the disease. The most common cognitive disorders in MS include diminished information processing speed, compromised word fluency, complex attention deficit and executive dysfunction.*

Methods: *In this mini review, we present the reader with the most common neuropsychological assessments for the evaluation of cognition in MS, addressing the question of cognitive relapse. Source of data presented in this review is PubMed search of the recently published literature on cognitive decline in MS.*

Results: *Patients with cognitive relapse often fail to meet diagnostic criteria for classical relapse in MS. Although, cognitive decline relates poorly to functional disability in MS, it correlates well with neuropsychological testing and with neuroimaging parameters of the disease.*

Conclusions: *Cognitive decline might be considered as additional indicator of MS activity, and therefore evaluated routinely, irrespective of clinical presentation. Brief cognitive assessment, with confirmed psychometric qualities, might be useful in detection of cognitive relapse in MS patient.*

Key words: *multiple sclerosis - cognitive decline - cognitive relapse*

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INTRODUCTION

MS is characterized by the neuroinflammation of central nervous system (CNS) that progressively leads to demyelination, axonal loss and neurodegeneration. As neuroinflammation declines with the disease progression, neurodegeneration leads toward brain volume loss and subsequent cognitive decline. The hypothesis on the combined effect of these pathophysiological mechanisms extends through the classification of MS phenotypes, according to the disease activity and progression (Lublin 2014). Recently, the challenge has been set to question if neurodegeneration might occur independently from the neuroinflammation or even considered as the primary cause of MS neuropathology. Regarding this question, neuropathological studies have detected an extensive axonal loss in normal appearing white matter and ongoing myelin destruction in cerebral cortex of progressive MS patients, without an inflammatory infiltration of immune cells (Trapp & Nave 2008, Abdelhak et al. 2017). Two main hypotheses were postulated to describe specific CNS lesions in MS: the inflammation-induced neurodegeneration, known as the outside-in theory, and the neurodegeneration-provoked inflammation, known as the inside-out hypothesis. The inside-out hypothesis denotes an independent degeneration of oligodendrocytes and axons, followed by microglial activation and subsequently invasion of inflammatory cells. On the other hand, the outside-in hypothesis implies that neuroinflammation induces demyelination, leading to axonal loss and subsequent neurodegeneration (Stys et al. 2012, Stadelmann et al. 2011). It is widely accepted that axonal loss is a major correlate of permanent functional disability in MS patients. Clinical symptoms of MS progression generally occur when threshold of axonal loss reaches the exhaustion of the compensatory mechanisms (Pérez-Cerdá et al. 2016). Declining neuronal reserve leads to brain atrophy, which is more pronounced in MS then in normal aging (Krieger & Sumowski 2018). There is significant interindividual variability of cognitive deficit in MS, due to the various compensatory mechanisms and a different cognitive reserve capacity (Sumowski et al. 2010). Cognitive dysfunction, associated with the axonal loss in strategic cortical areas is less likely detectable, but it occurs throughout the course of MS and in all clinical phenotypes. Total axonal loss in white matter of severely disabled MS patients' rates from 60-70%. (Pérez-Cerdá et al. 2016), but these pathohistological changes in CNS are not sufficient to clarify cognitive decline. Reported prevalence of mild to moderate cognitive decline ranges from 20 to 40%. Severe cognitive decline is more pronounced in progressive forms of MS, with almost 50-60% patients affected (Rao et al. 1991, Benedict et al. 2006, Patti et al. 2009, Glanz et al. 2007). Cognitive deficit poorly relates to functional disability, which is known as the cognitive

functional paradox. MS patient is subjectively unaware of the cognitive decline and underestimates the problem, mostly because functional disability is usually only attributed to clinical presentation or neuroradiological findings (Carone et al. 2005, Benedict et 2004).

COGNITIVE OUTLOOKS IN MS

Most common cognitive deficits in MS comprise diminished information processing speed and reduced working memory, both decreasing the ability to retain data and affecting a short-term memory (Drew et al. 2009, Owens et al. 2013, Genova et al. 2013, Chiaravalloti et al. 2013). Other common cognitive problems include executive dysfunction and word fluency impairment (Langdon 2010, Strober et al. 2009). Executive dysfunction is related to incompetent problem solving and compromised task planning. Frequently, patient has a difficulty initiating action and achieving an objective, or managing transitions to complete the task. Prolonged concentration is reduced and multitasking is generally impaired. Visual and spatial processing is affected, with problems in orientation and navigation. Perceiving new data is reduced, as well as the learning skills, thus hearing the information repeated, is often warranted. Further on, word fluency is affected, and patient's speech is incoherent (Langdon 2010, Strober et al. 2009). As multiple cognitive domains are concomitantly affected, activities of daily living and quality of life are frequently reduced. Although cognitive deterioration is equally impertinent as the relapse, it is often not a priority item in neurological assessment. Considering the negative impact of cognitive impairment, neuropsychological testing is recommended in MS patients. However, fatigue and depression should be considered during evaluation, since both account for the common comorbidities in MS and are often confounding factors with the negative impact on cognition. Fatigue is often mistaken for a cognitive deficit. It is subjectively described as tiredness and overall lack of energy, implying reduced ability to perform a long-term task. Depression affects almost the half of MS patients, and clinically depressed patients often experience working memory impairment or have trouble scheduling and performing tasks. (Goverover et al. 2005, 2010, Kalmar et al. 2008).

NEUROPSYCHOLOGICAL TESTING IN MS

Evaluation of cognition in MS patient is rarely considered as an integral part of neurological examination. It is usually performed only when a patient subjectively complains about reduced memory capacity or diminished attention and concentration (Cheng et al. 2010). The frequency and severity of cognitive problems in MS patients are usually evaluated through self-administered 15-item questionnaire, Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ) (Benedict et al. 2004). However, memory or attention deficit is not an actual predictor of cognitive dysfunction, because it might be influenced by the affective changes. Therefore, cognitive testing is mainly conducted by the neuropsychologist, who analyses results according to the clinical context, with regards to confounding factors, such as depression, fatigue and anxiety. However, it is recommended that neurologists should also conduct short neuropsychological evaluation, if not associated with an additional complex training and it is easy to perform in clinical settings. Common neuropsychological tests utilized in MS patients include Brief Repeatable Battery of Neuropsychological Test (BRB-N) (Bever et al. 1995) that is usually performed during the 45 minutes period, Minimal Assessment of Cognitive Function in MS (MACFIMS) (Benedict et al. 2002), completed through 90 minutes or Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) (Langdon et al. 2012, Benedict et al. 2012), that is accomplished during 15 minutes. In 2012, BICAMS was recommended by the consensus for the evaluation of cognitive dysfunction in MS patients, being recognized as simple, and sensitive test battery. BICAMS consists of Symbol Digit Modalities Test (SDMT) (Smith 1982) utilized for evaluation of processing speed, California Verbal Learning Test 2 (CVLT2) (Delis et al. 2000), for auditory verbal memory assessment and Brief Visuospatial Memory Test Revised (BVMTR) (Benedict 1997) for visual spatial memory assessment. Almost all MS cognitive batteries include SDMT and it is also recommended for a single use. According to BICAMS, SDMT is recommended for a quick cognitive assessment, if only five minutes was available. CVLT2 and BVMT-R are additionally performed, if a further ten minutes are available. The SDMT is based on task of coding symbol by number. It includes a reference key of nine symbols, each paired with a single digit. Symbols are arranged randomly in rows, located below the reference key. It has two versions of oral and written exam, but the oral version is commonly used. The subject is given 90 seconds to say the number that corresponds to each symbol. Due to its easy administration, high reliability and psychometric validity, SDMT has become the most popular test for cognitive evaluation of patient with MS. The CVLT2 is recommended for testing auditory verbal memory. It consists of 16- word list, arranged randomly, with the four words belonging to the same of the four semantic categories. The list of words is read aloud to the subject, five times in the same order. After each reading, subject is required to recall as many words as possible, regardless of order. The BVMTR is recommended for the visual memory evaluation. Subject is required to look at display with 6 geometric figures, that are presented for 10 seconds.

After the display has been removed, the subject is required to draw figures. Each figure is scored according to correct shape and position, from 0 to 2 points. There are 3 learning trials, so total score is 12 points. Alongside with SDMT, The Paced Auditory Serial Addition Test (PASAT) (Gronwall 1977) is another test, used for the evaluation of information processing speed. PASAT is utilized for the evaluation of speed needed for auditory information processing, and for the calculation ability. It is presented on audio-media with controlled rate of stimulus presentation. Auditory stimuli are single digits, presented either every 3 or every 2 seconds. Subject must add each new digit to the one that was presented previously. The test score is the number of correct sums given, out of 60 points possible. PASAT is integrated in the Multiple Sclerosis Functional Composite (MSFC) (Fischer et al. 1999) that consists of 3 examinations: The Timed 25-Foot (7.62 meters) Walk, a quantitative measure of lower extremity function, and the 9-Hole Peg Test (9-HPT), a quantitative measure of both upper extremities function. There are number of other neuropsychological tests, used in MS multicenter clinical trials for cognitive evaluation such as the MS-Cog composite outcome measure (Erlanger et al. 2014) that have proven to be feasible and warranted.

COGNITIVE RELAPSE

Clinical MS relapse is defined as a new, worsening or recurrent neurological symptom, that corresponds with disease activity and/or acute MRI lesions, occurs at least 30 days after the onset of a proceeding one, and lasts at least 24 hours, in the absence of fever or infection. Clinically, relapse is confirmed when the subject's symptoms are accompanied by an objective neurological change from the previous clinically stable state, determined by the Expanded Disability Status Scale (EDSS) assessment (Kurtzke 1983). Acute MRI lesions may or may not be accompanied by clinical symptoms, because neuroinflammation activity does not always lead to relapse or clinical symptoms. This silent MS activity without visible clinical manifestation is in focus of NEDA concept or 'no evidence of disease activity (Giovannoni et al. 2011, Rotstein et al. 2015). NEDA is generated to improve MS outcomes and optimize MS treatment. It is composed of three outcome measures: no relapses, no disability progression and no magnetic resonance imaging (MRI) activity (new or enlarging T2 lesions or gadolinium enhancing T1 lesions, which may represent "subclinical relapses") (Giovannoni et al. 2011, Vaneckova 2009). However, it is quite challenging to determine a cognitive relapse in MS patient with the change in mental status or in patient with cognitive dysfunction and with MRI evidence of relapse, but without clinical evidence of acute disease activity. The concept of NEDA is still evolving, but long term follows up showed that NEDA is strongly related to a better functional outcome over years later. In progressive MS, the concept of NEPAD, or 'no evidence of progression or active disease' is considered to be more appropriate than NEDA. In relapsing remitting MS, relapses are clinically important, and their frequency will guide treatment decisions. In progressive forms of MS, increasing disability is the main concern, and more emphasis is placed on slowing or preventing progression. The concept of NEPAD was introduced during efficacy evaluation of ocrelizumab (Wolinsky et al. 2018). Recent data suggest that MS patients with a cognitive relapse might be identified by SDMT. Monitoring of cognitive decline, before and during relapse period, might provide significant SDMT score change. If SDMT core declines during relapse and then recovers, observable change could be considered significant. Change of SDMT score by 4 points or 10% change is considered meaningful (Benedict 2017). Prospective study that evaluated cognitive impairment by SDMT, in relapsing MS patients and controls, distinguished the two groups, during a relapse, by 5 SDMT points. Several months later, the difference was reduced to 3 SDMT points. These results indicate, that it is possible to recognize MS patients with cognitive changes as part of a relapse, by using SDMT (Benedict 2013). SDMT evaluation in MS patients with relapse, provided the correlation of clinical and cognitive status. In the study of isolated cognitive relapse, 17 subjects from the group of 99 patients, were identified with the stable EDSS, but with a cognitive relapse, assessed by SDMT, and with positive MRI gadolinium enhancement, that correlated with the SDMT decline. After 6 months and 1 year of follow-up, recovery was only partial (Pardini et al. 2014). Compared by SDMT results, patients with relapse had a declined SDMT score by 2-3 points, after which they recovered almost to the control group level. The results of these studies showed that changes in SDMT were greater in relapsing patients, and that SDMT might be considered as a meaningful tool for detection of cognitive relapse (Morrow et al. 2011). Further on, SDMT is well correlated with MRI parameters of brain atrophy (cortical grey matter tissue loss, and third ventricle with or thalamic and hypothalamic fraction) (Sanfilipo et al. 2006, Stankiewicz et al. 2011, Schoonheim et al. 2008, Benedict et al. 2013, Bisecco 2015), thus measurement of cortex thickness correlates well with cognitive testing in MS (Amato et al. 2008, Filippi et al. 2010). Cortical lesions located in the frontal and mesial temporal lobes and anterior cingulum are associated with the cognitive deficit and fatigue. Lesions located in the deep grey matter in thalamus and hypothalamus area correlate well with the visual-spatial memory deficit and reduced information processing speed (Houtchens et al 2008, Mike et al. 2011).

CONCLUSION

Cognitive testing is often neglected in evaluation of MS patient. It is not a priority in clinical settings, and it is considered only concomitant to EDSS functional disability evaluation, although it has the same importance as clinical relapse or MRI neuroimaging parameters of disease activity. It is not even conducted systematically in clinical trials, and if implemented, it is defined only as the secondary or tertiary outcome measure. Neuropsychological testing should be performed routinely in all MS patients, as an additional indicator of disease activity, regardless of clinical or neuroimaging presentation (Kalb et al. 2018). Brief cognitive testing, with confirmed psychometric qualities such as BICAMS battery, proved to be a sensitive tool in detection of cognitive decline that might account for a cognitive relapse in MS. BICAMS testing provides short cognitive assessment in everyday neurological practice, and it includes set of short and easy-to-perform neuropsychological tests, that are accessible to neurologist without an expertise in neuropsychological training. Rationale behind this cognitive monitoring is prompt recognizing cognitive relapse, optimizing MS treatment and improving the quality of life in MS patients.

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Contribution of individual authors:

Marijana Lisak: design, literature searches, interpretation of data, manuscript writing.

Bruno Špiljak: literature searches; reference list writing according to the instructions.

Hanna Pašić: reference adjustment.

Zlatko Trkanjec: design, interpretation of dana.

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