Chapter

Cognitive Impairments in Early Multiple Sclerosis

Raphiq Ibrahim

Abstract

Over the past few decades clinical and research awareness has grown about the nature and prevalence of cognitive disorders in multiple sclerosis (MS). It is assumed that 65% of hospitalized MS patients develop cognitive impairments which have consistently demonstrated a pattern of decline in the following areas: attention working memory executive functions and verbal episodic memory. This chapter reviews the evidence for its associated comorbidities which may address early in the disease course that supports the importance for early recognition and management of cognitive impairment in MS before it becomes an irreversible entity. The focus is on three areas of inquiry: The first aims to provide a description of cognitive impairment in MS at all disease stages and in all subtypes. The second tried to evaluate the clinical imaging and neuroanatomical aspects. And the third focuses on cognitive assessment therapy and rehabilitation based on the literature.

Keywords: multiple sclerosis, cognitive impairment, comorbidities, assessment, imaging, memory disorder, therapy, rehabilitation

1. Introduction

Deficits of diseases of the brain have been extensively characterized in the last decades. However, few studies have examined their associated cognitive impairments. In the last decade, interest has focused on the cognitive impairments that develop following encephalitis (see, [1]) and multiple sclerosis (MS) [2, 3]. The symptoms of MS disease impairments were determined mainly by examining the hospital records of those previously admitted with degree of central nervous system damage (cerebral inflammation), who were assessed after detecting motor, and other neurological dysfunction. We now know that cognitive impairment associated with multiple sclerosis can have many faces, and like other symptoms of multiple sclerosis, the cognitive deficits are highly variable. Although cognitive impairment in MS impacts negatively on many patients at all disease stages and in all subtypes, full clinical cognitive assessment is expensive, requiring time and expert staff. In addition, standardized tests are not available for all languages and cultures. This chapter deals with these stages and subtypes, clinical assessment, imaging and neuroanatomical aspects, therapy, and rehabilitation based on the literature and subjective clinical experience and follow-up.

2. Background

Multiple sclerosis (MS) is a chronic disease affecting the central nervous system (including the brain, optic nerves, and spinal cord). It is characterized by the destruction of the insulating myelin layer of nerve fibers within the brain. The classical course of the disease evolves when the immune system attacks the nerve cells. Usually, the initial stage of the disease alternates between inflammatory autoimmune attacks on myelin by infiltrating T-cells and periods of remission and partial recovery, called relapsing-remitting MS (RRMS) [4]. Two major courses of multiple sclerosis have been described: an offensive course and the preliminary chronic course. The myelin sheath surrounds the nerve cells and serves the dual purpose of augmenting the conduction of nervous signals. Once the myelin sheath is damaged, nerve signaling is impaired, and this malfunction leads to various symptoms such as numbness, fatigue, weakness, blurry vision, and cognitive dysfunctions (high-level functions that include: information processing speed, attention, memory, and executive function). There is a broad-spectrum symptom, whose manifestation depends on the degree of brain damage and the neuroanatomical scattering. According to Lublin et al. [5], the frequency of relapses can vary from patient to patient. While most cases of RRMS are mild and the symptoms could last for a long time, it can be followed by a progressive stage of irreversible degeneration of demyelinated and exposed nerve cells, called secondary progressive MS (SPMS). In some cases, the disease is progressive from the onset. This type of MS is called primary progressive MS (PPMS). These destructive processes cause severe symptoms including blurred vision, loss of balance, poor coordination, slurred speech, tremors, numbness, fatigue, paralysis, and dysfunctions in memory and concentration. This chapter explores the way that MS affects high-level functions with a focus on memory and executive functions according to the stages and subtypes of multiple sclerosis.

3. Cognitive impairment in multiple sclerosis

Over the past few decades, clinical and research interest has grown about the nature and prevalence of cognitive impairment associated with multiple sclerosis. Cognitive impairment has been reported in all stages and subtypes of multiple sclerosis. The severity and type of cognitive impairment vary between individuals and can be observed in both early and progressive stages. The cognitive impairment, which is based on the findings of many studies, has consistently demonstrated a pattern of decline in the following areas: ability to maintain attention over time, retrieving information received after time delay, information processing speed, spatial visual perception, abstraction ability, and verbal fluency.

Prevalence studies of community and clinical samples indicate that 53–65% of hospitalized MS patients develop cognitive impairments [6]. Cognitive impairment contributes significantly to the patients' disability status, but there is no significant correlation between cognitive impairment and physical disability [7]. However, it is known that cognitive impairment increases morbidity in patients and is associated with a decrease in participation and functioning of daily life activities, such as driving, making medical decisions, adhering to treatment, and managing finances and work. Furthermore, cognitive impairment appears to be associated with increased unemployment rates and lower quality of life. For example, 7 years after diagnosis, only 54.4% of the MS population remains employed. This is associated with the

presence of cognitive impairment (CI) at the time of, or shortly after, MS diagnosis [8]. The most common cognitive deficits in MS are slowed cognitive processing speed and episodic memory decline in addition to difficulties in executive function, verbal fluency, and visuospatial analysis. Cognitive decline often emerges early in disease, but impairment is more prevalent and may differ qualitatively (e.g., working memory deficits) among patients in progressive stage.

In view of the fact that memory disorder is one of the most common symptoms reported in MS patients, it is obvious that this chapter focuses on this and related function according to stages and subtypes of multiple sclerosis. As the nature and source of memory impairment are still in debate in the professional literature, the main question in this regard is whether memory loss is caused as a result of a deficit in acquisition process, encoding deficit, or retrieval ability. In a number of studies, it has been found that while MS patients demonstrate relatively normal short-term memory functions, they show difficulties in remembering long-term information, and the difficulties increase as they are more exposed to various distractions (interference) [9, 10]. In the field of verbal memory, difficulties in spontaneous retrieval are described with an improvement in the performance of recognition tasks. In examining nonverbal memory tasks, shortages in the recall of visual information were demonstrated. It has been found that when MS patients are compared to control subjects, they show poorer performance in remembering practical forms and in remembering their spatial location [9]. Ron et al [10] even argued that memory impairments in MS patients are more prominent in the visual stimuli than in the verbal stimuli. In the same study, a correlation was found between cognitive decline and the extent of brain damage and the duration of the disease. Regarding the effect of different disease characteristics on memory functions, [11] found that MS patients in a progressive stage show deficiency in information acquisition. However, their performance was not found significantly different in the identification tasks than those of the control subjects. Most of the studies conducted among the MS patient population were built on the awareness level paradigm when acquiring new information. A later study conducted by [12] examined memory functions under different conditions: explicit vs implicit memory. In their study, they used the task of completing the roots of the word, in order to separate explicit and implicit learning. It was found that while MS subjects diagnosed as having cognitive decline, they showed normal performance in tasks that tested for non-intentional learning and poor performance in tasks that test intentional learning. MS patients not diagnosed as suffering from cognitive decline performed all tasks at a level similar to that of a group of control subjects. This study reinforces the assumption of [13] that an *emplicit* process of acquiring information is based on conserved cortical structures, with a deliberate learning process more closely linked to the subcortical structures. Namely, the main cause of implicit learning disorder in MS patients suffering from cognitive decline is due to a disconnection between the cortical regions and subcortical structures. In regard to performance in autobiographical memory in multiple sclerosis [14], found that close to 66% of MS patients exhibit autobiographical memory impairments, with the ability to remember episodic autobiographical events being more impaired than the ability to remember semantic autobiographical information. It should be noted that this study examined patients at an advanced stage of the disease a factor that may explain the severity of the deficiencies that were demonstrated. A supporting result came from clinical studies with head injury patients. De Sonneville et al. [15] used a neuropsychological battery designed to test for split attention, ability to focus attention, ability to maintain an attention over time, and executive functions. Significant deficiencies

were found in MS patients compared to control group in all areas examined. In addition, patients in the progressive disease stage were significantly inferior to the group of patients with relapsing-remitting disease stage. Along with the previous results demonstrated by [16], a significant correlation was found between the subtype and duration of the disease and the decline in cognitive functions. The Paced Auditory Serial Addition Test (PASAT) task is the most used task in trying to detect defects in the areas of working memory and information processing, and it has been included as a central part for these purposes in a specific battery designed for MS patients (MSFC). Fisk and Archibald [17] pointed out a certain difficulty in interpreting the results of this test because an increase in the level of complexity of the task leads to an executive strategy of chunking, which may disguise the true ability. Reporting bugs in areas that test visual information processing, Laatu et al. [18] used visually displayed objects in order to detect whether there is a deficiency in specific information processing stages that may be present in MS patients. The results revealed that MS patients with a diagnosed cognitive decline had difficulty with tasks that required the distinction and identification of visual forms (early stage of information processing) and the ability to associate objects according to semantic-lexical information. Due to the great variability between different patient groups, it has been hypothesized that even cognitively normal MS patients may have difficulty in processing visual information.

It is important to note that standard neuropsychological tests in some cases fail to detect clinically emergent cognitive deficits and cognitive complaints reported by patients, which can be confounded by other subjective symptoms (comorbidities) (see, [7]). That is, cognitive functions can be affected by emotional stress, depression, sleep disorders, menopause, aging, or fatigue. Furthermore, some prescription treatment drugs can impair cognitive performance. But this issue falls out the scope of this work.

3.1 Cognitive assessment

Although a high incidence of CI is recognized in advanced stages of MS, the point at which CI first appears is not clearly defined. It is likely that the disease is not diagnosed in the early stages even after neuropsychological assessment, and indeed the presence of CI does not seem to be highly correlated with the its duration.

However, accurate measurement is an important aspect of comprehensive patient management. Routine clinical evaluation by the neurologist lacks sensitivity in detecting CI, compared to standard neuropsychological tests. This is due to both patient underreporting and the use of brief cognitive assessment measures in clinical practice. The most commonly used are the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessments, which test mainly for cortical functions; short-term memory loss, aphasia, apraxia, construction, and orientation, areas that are usually affected in dementia, but not in MS. With only limited testing of attention and executive functions, they are not sensitive or specific tests for CI in MS.

There is no single test that measures cognitive problems in MS. Some screening tools are available, but none of them are perfect. Research studies often use the PASAT (Paced Auditory Serial Addition Test). It takes a few minutes and consists of a task that measures addition and repetition of previous numbers. It may be moderately stressful. A formal neuropsychological examination is the best test for assessing disturbing cognitive changes in MS. During a neuropsychological evaluation, multiple tests are used to measure memory, attention, and many other parts of cognition. The speed of cognitive processing is usually estimated as the amount of work done within a time limit (e.g., the number of items completed). There are number of cognitive batteries

developed for MS, include tests of processing episodic memory (e.g., the amount of information learned and remembered: words, visual stimuli), speed, memory, and other functions managed separately by skilled professionals. We critically reviewed the most common tasks and identified the Symbol Literature Test (SDMT), the Short Vision-Spatial Memory Test (BVMT-R), and the Selective Reminder Test or Verbal Learning Test in California-II (CVLT-II) as the tasks that are most sensitive and the most available today for cognitive monitoring in multiple sclerosis. SDMT is the most sensitive, probably because good performance depends on a number of functions affected by MS (mainly processing speed, but also memory and visual scanning).

Although MS is short on neuropsychological standards, the need for even 15 minutes of one-on-one testing for each patient is impractical, so cognitive monitoring is not part of standard MS treatment. A computerized test may be a worthy alternative to a conventional paper and pencil evaluation. For example, the Processing Speed Test (PST) is a tablet-based test designed according to the SDMT (and part of MS Performance). The quality of the battery used for assessment in MS should be determined based on the following: standardization, ability to differentiate the MS population from controls, test-retest reliability, availability of normative data, and learning effects.

The Brief Neuropsychological Test of Repetition Battery (BRB-N) consists of five different neuropsychological tests: selective recall, spatial recall, symbolic digit modes, rhythmic serial auditory addition, and word list generation tests. It has been validated as a sensitive measure of early CI in MS, with a sensitivity of 71% and a specificity of 94%, in distinguishing cognitively impaired from cognitively intact MS patients. It takes 45 minutes to administer and requires staff trained in neuropsychology. PASAT is particularly subject to learning effects when repeated, which usually do not stabilize until repeated at least three times in a participant. Both are the most commonly used and validated neuropsychological batteries for MS. They are comparable in their discriminative power, with equal abilities to discriminate between MS patients and healthy controls. Because both are time-consuming and require specialized materials and experienced neuropsychologists to administer and interpret, they are not used in routine clinical practice.

A diagnosis of probable mild-to-moderate cognitive impairment may trigger a person with MS to engage in a more "brain-healthy" lifestyle, if they have not already done so [7]. Marrie and Horwitz [7] claimed that although the interaction between comorbidities and chronic diseases is strong, the effect of comorbidities receives little attention in many chronic diseases. Patterns of cognitive impairment in multiple sclerosis and clinical assessment are present in all subtypes of MS, but are more common and more severe in progressive rather than relapsing MS.

To summerize, MS can induce different types of damage to the cognitive system. Although the ability to detect cognitive difficulties has improved over the past few years, there are many patients who are not diagnosed. Morever, in patients with multiple sclerosis and cognitive impairment, the full etiology remains unclear, as little is still known about their relative contribution to the underlying process of cognitive impairment. There is also a poor correlation between symptoms of cognitive impairment and conventional MRI measures of structural damage. At present, neurologists perform short assessments as a screening tool for cognitive impairment in MS. This is because a formal cognitive assessment done by neuropsychologists may be expensive and require several hours, expert staff, and special equipment. Furthermore, the neuropsychological assessment should take into account comorbidity and distinguish between cognitive impairment and other causes of perceived impairment, including anxiety, depression, and quality of life. Neuropsychological batteries yield quantitative

values, and impairment is generally defined as performance below the selected threshold (e.g., 1.5 SD below norm). However, the definitions of impairment have changed between studies, affecting the prevalence of impairment. Future work should better characterize groups as those with isolated or combined deficits (phenotypes, e.g., impaired memory but intact speed; impaired speed and memory) and use purer indices of each cognitive domain (e.g., latent variables or complex domain scores).

3.2 Imaging and neuroanatomical aspects of CI in MS

Recent developments in magnetic resonance imaging (MRI) techniques show a better association with CI than conventional measures of demyelination and offer insights into its pathogenesis. The literature suggests patterns of CI in MS associated to radiological findings. The focus is particularly on the evidence in the early stages of MS after diagnosis.

In fact, there is an increasing arsenal of function-based MRI assessment protocols (e.g., functional and effective connectivities (EC) and the generation of dysconnectivity maps) providing insight into the causal relations that may be impaired [19]. Effective connectivity (EC) estimations as derived from fMRI allow quantification of information flows in neural networks. Hence, EC is able to explore causal effects between cortical areas, which are highly relevant for biological network behavior and can be traced longitudinally to depict brain reorganization processes in brain diseases [20, 21].

The first evidence for the existence of cerebral compensatory processes in multiple sclerosis was received about four decades ago. In 1984, Mintun, Raichle, Martin, and Herscovitch examined a patient with a right demyelinating focus documented on a CT scan. This focus was demonstrated as a hypometabolic region on PET examination and was accompanied by a hypermetabolic region in the left hemisphere. There are neuroanatomical correlations of existing cognitive impairments (e.g., thalamus), but it is unclear whether such correlations are directly underlying the impairments or are reliable proxies for total (or other) brain damage, mediating links to cognition [22]. According to Ross and Ebner [22], the thalamus is very sensitive to retrograde degeneration and has a better scan-to-scan reliability than other structures. The thalamus volume constitutes a good measure of disease load across patients with variable central nervous system damage even it does not directly underlie a specific deficit (e.g., memory). In that regard, a large prospective longitudinal study with multimodal neural imaging needed to carefully document temporary correlations of specific cognitive impairments that arise with changes in specific brain structures and functions, thus informing advanced models of disease-related impairments that will help identify therapeutic goals. Other researchers have suggested that longitudinal work may help establish transverse associations between memory impairments and changes in the hippocampus [23]. There is also a growing body of literature of neurostimulation employed for memory improvement to enhance lateralization and functional connectivity [24]. Veréb and his colleagues [24] confirm previous descriptions of Resting State Networks[1] (RSN) dysfunction in relapsing-remitting MS and show that altered functional connectivity lateralization patterns of RSNs might contribute to cognitive performance and structural demodulation even in patients with mild clinical symptoms.

[1] Resting-State Setworks (RSNs) refer to distant brain regions display synchronous BOLD signal oscillations, testifying to functional connectivity between regions and forming intrinsic functional networks. RSNs are related to cognition and their alteration has been linked to various brain pathologies.

Huber et al. [25] examined a group of MS patients using neuropsychological tests and MRI. They found that only 28% of patients met the criteria for dementia, but the number and location of cortical lesions were no different from dementia patients compared to 72% of non-dementia patients. A further study by Steffan [26] using fMRI found differences in activation patterns when performing an attention task in MS patients compared to controls. In control subjects, an activation focus was found in the right frontal area, whereas in MS patients, the activation was more diffuse and was observed in both the right and left frontal areas. This finding is interpreted as an expression of a compensatory process that plays an important role already in the early stages of the disease (Mintun, Raichle, Martin & Herscovitch, 1984). In a similar technique used by Zivadinov and his colleagues [27], they found an indication of metabolic imbalance in brain tissue, even in disease stages that had no clinical manifestation (without permanent neurological damage). Furthermore, a correlation was demonstrated between the degree of brain parenchyma damage and cognitive impairments, demonstrating important aspects that may contribute to both understanding the disease itself and the nature of its effects on cognitive processes. In general, even today we are still talking about the following factors and their important role in the pathogenesis of cognitive decline in MS: several brain lesions, intensity of pathological damage to brain tissue around lesions (parenchime), and axonal loss. Both clinical and associated radiological findings will apply particularly to processes involved in the early stages of MS after diagnosis.

4. Cognitive therapy and rehabilitation

Neuropsychological rehabilitation is currently the mainstay of treatment for cognitive disorders in multiple sclerosis. Training that improves cognitive function can significantly improve the quality of life of a person with multiple sclerosis. There is also a chance to support prevention of cognitive decline through, among other things, interventions and healthy lifestyles that promote brain maintenance. In cases of relapsing-remitting attacks, drug treatments for multiple sclerosis may help stabilize and possibly improve cognition if the disease is caught early enough.

The literature shows that rehabilitative cognitive therapy may be beneficial to the overall picture and make it easier to deal with difficulties in daily life. However, there are few controlled studies on the effectiveness of MS treatment, and these studies have provided limited evidence that disease-modifying therapies are effective in treating cognitive dysfunction. In recent research, Moreau and his colleages [28] asked if cognition can be enhanced via training. On the one hand, there is potential to prove the effect of intervention with applications ranging from developmental disorders to cognitive aging, dementia, and traumatic brain injury rehabilitation. On the other hand, it is difficult, because establishing clear evidence for an intervention is particularly challenging in psychology. Due to logistic shortcomings or to common difficulties in disguising the underlying hypothesis of an experiment, it is not always feasible to assure double-blind randomized controlled experiments. These limitations have important consequences for the strength of evidence in favor of an intervention [28]. Hämäläinen and Rosti-Otajärvi [29] based on rehabiliation and traning program concluded that there are positive effects of neuropsychological rehabilitation in MS.

Lizanne Evavan den Akker and her colleagues [30] tested short and long-term effects of cognitive behavioral therapy (CBT) for the treatment of MS-related fatigue. They performed a meta-analysis of the effectiveness of CBT for fatigue in patients

with MS. The results indicated a moderately positive short-term effect of CBT for the treatment of fatigue in patients with MS. However, this effect declined after cessation of treatment. The authors suggested that since the short-term effect of CBT on MS-related fatigue is positive, more research is needed to develop interventions that maintain these short-term effects for the long term.

Regarding the nature of the effect obtained following cognitive therapy, work by Penner et al. [31] used neuroimaging techniques to study the effects of cognitive rehabilitation in MS including task-based fMRI across multiple realms of cognition (e.g, executive functioning, attention, and processing speed). MS patients were examined using fMRI before and after cognitive practice in attentional tasks. The results of the study indicated that after the practice, there was an increase in activation that was more pronounced in the parietal and frontal areas, but the degree of activation was not correlated with an improvement in the performance of tasks. Apparently, performance improvement depends on the capacity of the brain to establish new functional pathways.

Hayes and his colleagues [31] reviewed 13 studies with 839 participants involving various types of fall interventions, most comparing an exercise intervention with no intervention or two or more fall prevention interventions. They tried to explore whether 1. people with multiple sclerosis (MS) who received interventions to reduce falls show better fall outcomes than those who received no treatment?2. different types of falls interventions result in different outcomes for people with MS. Based on the results, they concluded that "there is some evidence in favor of exercise interventions for the improvement of balance function and mobility. However, this must be interpreted with caution as the results represent data from a small number of studies." Looking at the whole picture, we require a science of cognitive rehabilitation capable of yielding high levels of evidence. Toward this end, theoretical models of MS-related cognitive dysfunction and ways to identify mechanisms of action to treat deficits must be developed. Finally, standards for a priori reporting of methods must be upheld for cognitive rehabilitation, including greater transparency for outcomes. In this regard, cognitive rehabilitation researchers are directed to Simons et al. [32] for a thorough discussion of essential guidelines for the conduct of high-quality cognitive intervention trials.

5. Conclusions

Several neurological disorders have a positive association with MCI cognitive deficits. This chapter reviews this association in the case of multiple sclerosis (MS), covering MS subtypes and staging, clinical and imaging assessments, and therapeutic options. MS is invariably progressive, though mild symptoms may persist for variable intervals, a fact of notable interest to patient and clinician alike. The chapter's focus on high-level cognitive function and memory-related deficits affords a unique perspective not often found in MS research with an exploration of MS-specific, memory impairments that, tragically, occur at all MS stages. The discussion of the evolution of MS with its consideration of the extent and character of these impairments as a function of stage provides a valuable backdrop against which to distill clinical diagnosis. MS subjects, as noted, can display MS-specific sets of deficits, [normal performance in non-intentional learning tasks and poor performance in tests of intentional learning; the demonstration of relatively normal short-term memory functions, while having difficulties in recollection of long-term information]. Based on these unique footprints, this chapter makes the inference that the implicit learning

disorder observed in MS patients suffering from cognitive decline is due to a disconnection between the cortical regions and subcortical structures, a point of interest for targeting causal factors. It was proven that in multiple sclerosis (MS), there are physical and mental comorbidities, and adverse health factors such as smoking and obesity are common and can affect the disease. These comorbid diseases and lifestyle factors affect clinical manifestation, the disability progression, and health-related quality of life [7]. People with MS can benefit from maintaining a healthy weight, keeping up regular exercise, getting enough sleep, and staying psychologically well. This brain-healthy lifestyle could protect against further progression of MS. This chapter recommends that numerous clinical batteries can be expected to facilitate the choice of batteries optimally suited to the MS subject. These recommendations should be separate but related to and joined to the recommendation of Langdon et al. [33], for a brief International Cognitive Assessment for Multiple Sclerosis that will take into account the caveats and the comorbidities mentioned.

Author details

Raphiq Ibrahim
Edmond J. Safra Brain Research Center for the Study of Learning Disabilities, University of Haifa, Israel

*Address all correspondence to: raphiq@psy.haifa.ac.il

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