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Effect of Cognitive Impairments in Multiple Sclerosis on Caregivers' Quality of Life: A Review

Multipl Sklerozda Bilişsel Bozuklukların Bakım Verenlerin Yaşam Kalitesi Üzerindeki Etkisi: Bir Gözden Geçirme

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ÖZ

Denge problemleri, yorgunluk, uyuşukluk, görme kaybı ve tremor gibi semptomları olan multipl skleroz (MS), bilişsel işlevlerde de bozulmaya yol açmaktadır. MS hastalarının önemli bir kısmı bellek, dikkat, bilgi işleme ve yürütücü işlevler de dahil olmak üzere çok sayıda bilişsel alanda zorluk yaşamaktadır. Yaşanan bu zorluklar kişilerin günlük yaşamını da olumsuz yönde etkilemektedir. MS'deki bilişsel bozulmanın araştırılmasıyla birlikte, bu becerilerdeki eksikliklerin hem hastaların kendileri hem de bakım verenlerin üzerindeki etkisi fark edilmeye başlanmıştır. Bu çalışma, MS hastalarında bilişsel bozukluklara bakım verenlerinin yaşam kalitesi bağlamında genel bir bakış sunmayı amaçlamaktadır. Çalışmaların ortaya koyduğu üzere, bilişsel becerilerdeki bozulma hem hastaların hem de bakım verenlerin yaşam kalitesini olumsuz yönde etkilemektedir. Bu bulgular ışığında, MS hastaları ve bakım verenleri için bilişsel becerilerin günlük yaşama entegrasyonda önemli bir role sahip olduğu sonucuna varılmaktadır.

Anahtar sözcükler: Multipl skleroz, bilişsel bozulma, bakım veren, yaşam kalitesi

ABSTRACT

Multiple sclerosis (MS), which has symptoms like balance problems, fatigue, numbness, loss of vision and tremors, also leads to impairment in cognitive functions. Most patients with MS have difficulties with numbers of cognitive domains including memory, attention, information processing and executive functions. These difficulties also negatively affect the daily life of individuals. As cognitive impairments in MS have been investigated, the impact of these difficulties on both the patients themselves and their caregivers has begun to be recognized. The aim of this study is to overview cognitive impairment in MS patients within the context of caregiver quality of life (QoL). As studies have shown, impairment in cognitive abilities negatively affects the QoL of both patients and caregivers. In conclusion cognitive abilities have an important role in the integration of MS patients and their caregivers into daily life.

Keywords: Multiple sclerosis, cognitive impairment, caregiver, quality of life

Introduction

Multiple Sclerosis (MS), characterized by the formation of extensive lesions or plaques in the brain and spinal cord, is a progressive neurological disease (Chiaravalloti and DeLuca 2008, Goverover et al. 2017). It is the most prevalent chronic disabling disease of the central nervous system (CNS), affecting 2.4 million people worldwide (Jellinger 2024). In 2022, the prevalence of MS in Turkey was determined to be 96.4 per 100,000 and was categorized as moderate risk (Öztürk et al. 2024). It often affects young adults aged 20 to 40 years (Naseri et al. 2020).

Although the incidence rate continues to increase worldwide, the underlying cause of the disease remains uncertain. The fact that MS is caused by an interplay of environmental and genetic variables demonstrates the disease's multifaceted and intricate character (Fenu et al. 2008). MS patients may have various neurological signs and symptoms due to white matter lesions that occur with sudden attacks. It includes many symptoms such as muscle strength, coordination, balance, visual and cognitive impairment (Beer et al. 2012). Therefore, it has a variety of symptom clusters including motor, cognitive and neuropsychiatric (Chiaravalloti and DeLuca 2008). These symptoms can be classified as primary (symptoms that are a consequence of demyelination in the CNS), secondary (symptoms that are a consequence of the primary symptoms) and tertiary (symptoms

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resulting from the presence of a chronic form of the disease) (Goverover et al. 2017). Bowel and bladder problems, ataxia, fatigue, vision, cognitive problems, sexual problems, speech and swallowing difficulties and tremor are included in the list of primary symptoms while loss of balance, decreased activities of daily living and consequently depression and anxiety may be part of the secondary symptom cluster. Tertiary symptoms are result of social and psychological consequences like social isolation or reactive depression (Ben-Zacharia 2011). All these three clusters of symptoms lead to progressive limitations in the functioning of daily life. Therefore, a decrease in quality of life (QoL), which is likely to be caused by reductions in their functionality in daily life, is reported by MS patients. The impact of QoL in patients is affected by various factors including age, education, social support, and employment (Gil-González et al. 2020). Depression and fatigue are also associated with low QoL scores in patients with MS (Amato et al 2001; Drulovic et al. 2007). A study conducted in Turkey also showed that fatigue and depression strongly influence QoL of MS patients (Tanrverdi et al. 2010).

As the disease progresses, physical or cognitive impairments become more prominent, and patients require more personal support (Graves et al. 2023). Approximately 30% of people with MS usually need daily help from another person, in other words a caregiver. Informal carers, such as partners, siblings or friends, account for 80% of caregivers (Katsavos et al. 2017) and psychological well-being of these people is also affected by disease progression (McKeown et al. 2003). In a study comparing carers of Alzheimer's and MS patients, Dewis and Niscala (1992) found that both groups of carers experienced four times more stress symptoms than the general population. Therefore, it is obvious that the disease has a negative impact on both the person with the disease and their caregivers and especially affects the QoL (Gregory et al. 1996, Aronson 1997).

In the present review, the aim was to examine the effect of cognitive impairments on QoL of MS caregivers. It is critical to understand the impact of cognitive impairment on patients and caregivers in terms of adaptation to daily life of individuals diagnosed with MS. Although there are many studies on multiple sclerosis in the literature, studies on caregivers are limited. This study examines the factors that contribute to the care burden of caregivers, especially cognitive functions, and provides information on cognitive dysfunctions observed in patients with MS.

Cognitive Impairments in MS

According to neuropsychological studies, 43% to 70% of people with MS have impairments in various cognitive functions including memory (Beatty et al. 1996, Oreja-Guevara et al. 2019), executive functions (Foong et al. 1997, Macías Islas and Ciampi 2019), abstract thinking (DeSousa et al. 2002), information processing (Diamond et al. 1997, Grzegorski and Losy 2017) and attention (Winkelmann et al. 2007). Even though there are no neurological impairments in the early stages of MS, cognitive deficiencies may still manifest (Benedict et al. 2020). These deficiencies cause significant functional impairments in their daily lives at work and at home. Therefore, the assessment of patients' cognitive deficits is valuable for understanding the underlying pathology of the disease.

Memory and attention are the first cognitive abilities to be affected (Amato et al. 1995) while semantic fluency may decline more often than previously thought, especially in people over 50 years of age (Brandstadter et al. 2020). In addition to well-studied cognitive functions like attention and memory, studies on visual-structural and visual-spatial skills are insufficient and inconsistent (Winkelmann et al. 2007).

One of the negative effects of impaired cognitive functions on the patient is unemployment (Honan et al. 2015). It is reported that approximately 50% of MS patients become unemployed within ten years following the diagnosis (Morrow et al. 2010). Several studies have addressed that scores on neuropsychological tests predict work-related outcomes such as unemployment and lower working hours (Raggi et al. 2016, MacAdam et al. 2023). Especially, working memory deficits particularly have been shown to be linked to work-related difficulties (Raggi et al. 2016). In addition to unemployment and impact on activities of daily living, cognitive impairment is significantly associated with problems in social and family relationships (Mitchell et al. 2005). Accordingly, all of these have the potential to negatively affect a person's QoL.

Memory

Since the 1980s, research has shown that memory is one of the most common cognitive dysfunctions (Winkelmann et al. 2007). Approximately 40 to 65 % of patients struggle with moderate memory impairments, while 30 % of these patients have a more severe memory impairment (Arnett and Strober 2011). Changes in MS mostly affect declarative memory, which is involved in conscious recollection and recovery of information about one's own experiences and world knowledge while implicit memory is typically preserved (Oreja-Guevara et al. 2019).

While it was previously thought that memory deficits were caused by impairments in information retrieval, it is now believed that they are the consequences of impairments in learning information (Chiaravalloti and DeLuca 2008). They generally need more repetitions to learn the information (Trenova et al. 2016). This impairment in learning also affects prospective memory of patients (Rendell et al. 2007).

Both visual and verbal memory are reduced in people with MS; however, the impact of verbal memory deficits is likely to be more severe and prominent in the course of the disease (Rogers and Panegyres 2007).

Executive Functions

"Executive functioning" refers to composed of cognitive skills that include organizing, planning, conceptual reasoning and directing resources effectively required for complex goal-directed behavior and adjustment to demands or changes in the environment (Chiaravalloti and DeLuca 2008). In patients with MS, impairments in executive functions can be present in up to 19% of patients, albeit less frequently than memory deficits (Rao et al. 1991). The lack of skill in conceptual reasoning appears to be a common feature of MS (Rogers and Panegyres 2007). Deficits in set shifting (Mahler 1992) and concept formation (Beatty and Monson 1996) have been particularly highlighted.

Information Processing

Working memory and processing speed are two components of information processing efficiency that are both affected in MS patients (Migliore et al. 2018). According to studies, 40-70% of MS patients have impaired information processing speed. (Migliore et al. 2018). It has been asserted that slowed processing speed is one of the first identifiable cognitive symptoms of MS (Van Schependom et al. 2015). The patients have considerably longer simple and complex reaction times as well as slower memory scanning speeds (Rogers and Panegyres 2007). The decrease in information processing skills causes patients to be unable to fulfil social and professional requirements in their daily lives (Jongen et al. 2012).

Attention

Multiple components of attention are affected in MS, including selective, sustained, and divided attention (Oreja-Guevara et al. 2019). Impairment of sustained attention is more typical, whilst deficits in divided attention —the ability to focus on multiple tasks simultaneously have also been reported (McCarthy et al. 2005). Therefore, the main complaints received from MS patients are that they find it hard to follow a conversation or television show, maintain a task at work, or to focus on one thing when there are other distracting stimuli around (Oreja-Guevara et al. 2019). Extensive studies involving MS patients have consistently shown impairment on complex attention tasks (Rogers and Panegyres 2007), whereas their simple attention activities are mostly intact (Chiaravalloti and DeLuca 2008).

Factors Affecting Cognitive Dysfunction in MS

Cognitive impairment in the early onset of MS may be a marker of future disease development or the impact of potential preventive interventions; therefore, investigation of affecting factors is crucial. The presence and progression of cognitive dysfunction linked to MS are diverse. Numerous factors, including the duration and severity of physical impairment, as well as the onset of disease, have been linked to an increase in cognitive impairment (Patti 2008). The evidence on the course of the disease is more consistent (Wallin et al. 2006) while the evidence on the link between duration and cognitive impairment is contradictory (Winkelmann et al. 2007).

Cognitive impairment in MS patients often occurs throughout the progression of the disease but may also be detected at the initial presentation (Winkelmann et al. 2007). It is suggested that in the early stages of MS, cognitive impairment is observed in 26–54% of individuals (Achiron and Barak 2003). On the other hand, even if cognitive impairment is not present at an early stage, it is likely to appear and progress in a significant number of patients over a long follow-up period. In a longitudinal study of 45 patients with early-onset MS followed for 10 years, Amato et al. (2001) found that 74% of patients had no cognitive impairment at baseline, 8% had mild impairment and 18% had moderate impairment. After a 10-year follow-up, 44% of the patients who were re-evaluated had no cognitive impairment, 34% had mild impairment and 22% had moderate impairment. The findings of another longitudinal study showed that patients with cognitive decline worsened their cognitive dysfunction within 3 years (Kujala et al. 1997).

Apart from the course and duration of the disease, individual differences such as age and gender also have an impact on cognitive impairments in MS (Benedict and Zivadinov 2011). It is commonly accepted that aging increases the risk of cognitive loss. In the studies with MS patients, age was found to be significantly correlated to a higher rate of decline on neuropsychological tests (Amato et al. 2010). Many other factors such as lifestyle and associated increased cholesterol (Andaloro et al. 2021) and cardiovascular risk (Reiaet al. 2021) have been shown to be implicated in MS and cognitive deficits in MS. Sanaie et al. (2024) suggested that serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL) are linked to cognitive outcomes. In support of this, studies have shown that dyslipidemia, triglycerides and cholesterol are negatively associated with cognitive function score in MS patients (Andaloro et al. 2022). In addition, lower serum 25-hydroxy-vitamin D levels (Spiezia et al. 2023) and insulin resistance (Ayromlou et al. 2023) were also found to exacerbate cognitive impairment in MS patients.

It has also been investigated whether cognitive impairment in MS has a genetic basis. In particular, research has focused on the APOE gene, which has a role in Alzheimer's disease and is associated with cognitive functions. In addition to neurodegenerative diseases this gene is also associated with cognitive decline among healthy elderly people (Mahley and Rall 2000). However, findings on the association of the APOE gene with cognitive impairment in MS are conflicting. Aside from APOE, the link between genetic variation in brain-derived neurotrophic factor (BDNF) and cognitive performance in MS has been examined, and some polymorphisms have been reported to have a protective effect on cognitive aspects (Zivadinov et al. 2007). Genetic predisposition to MS may cause changes in brain structure, such as a reduction in gray matter (GM) volume, and may impair cognition without apparent disease (Ikram et al. 2017).

Some of the recent studies have focused on telomere biology and its relationship with various diseases. Short telomers have been identified as markers for several chronic neurological and inflammatory disorders (Smith et al. 2019). Some molecular biomarkers for MS are also associated with telomere length. Telomere shortening has been associated with elevated levels of certain proteins that are associated with a higher conversion rate from chronic isolated syndrome to relapsing remitting MS (RRMS) type (Hecker et al. 2021).

Problems Encountered by MS Caregivers

People with MS may become functionally dependent on others since they are unable to manage everyday life tasks on their own in the latter stages of the disease or exacerbations periods (Topcu et al. 2016); therefore, they may need caregivers. The progressive and unpredictable character of MS makes caring for individuals with the disease extremely demanding on caregivers, and it is acknowledged that doing so may put their health and well-being at risk (Topcu et al. 2016). Consequently, caregivers may ignore both their own needs and the needs of the patient (Penwell-Waines et al. 2016). Many studies in the literature show that caregivers of people with chronic illness, including MS caregivers, are at risk of experiencing serious “burdens” (Tramonti et al. 2019). Potential challenges for caregivers include physical and financial strain (O'Brien, 1993), feelings of pessimism, fatigue and anxiety (Knight et al. 1997), cognitive difficulties (Chipchase and Lincoln 2001) and decreased QoL (Katsavos et al. 2017).

Several factors have been demonstrated to contribute to the care burden, such as the level of impairment of a patient, the caregiver's age and health, the availability of support, and the caregiver's perception of uncertainty (Corry and While 2009). As the burden of care rises, caregivers are likely to suffer challenges relating to their physical or mental health, along with economic and social problems. (Dayapoğlu and Tan 2017). In addition, it is also suggested that caregiver burden affects the lifestyle of caregivers (O'Brien 1993). Generally, caregiver burden requires changes in personal plans like holidays or work and it can also cause disturbances in sleep patterns (Khan et al. 2007). Sleep disturbances, changes in daily life plans and physical and psychological changes are likely to result from the burden of disease all combine to have a negative impact on the caregiver's QoL.

In addition to these factors, MS patients' cognitive deficiencies have a considerable impact on the disease burden. Cognitive abilities are very important for an individual to perform daily activities. Therefore, impairment in cognitive functioning leads to a significant loss of autonomy and a reduced QoL (Sharac et al. 2010). The physical and cognitive difficulties of people with MS are reported to increase their usage of health services (Marrie et al. 2015), which also may have an impact on their caregivers. Several studies have found that the progressive decline in cognitive functioning of the patient substantially increases the burden of the caregiver.

Cognitive impairment and neuropsychiatric symptoms found in MS cause emotional and social distress in caregivers (Figved et al. 2007). Previous research has demonstrated that MS patients' impaired ability to information processing speed results in their inability to keep up with social and occupational expectations, which may eventually lead to social isolation (Jongen et al. 2012). MS caregivers reported that cognitive impairments cause relationship problems like diminish communication (Bogosian et al. 2009). All of these are likely to affect the burden of disease on the patient's carers. Chipchase and Lincoln (2001) found that impairments in everyday memory performance are associated with carer strain. In that study, carers reported that perceived strain resulted from impairments in memory, and they suggested that as a result of this impairment, the time they spent with themselves decreased and their mood was affected, and this affected their sympathy for the patient.

In a detailed study, which examined the impact of impairments in cognitive skills on caregiver's health-related QoL, the researchers evaluated patients' cognitive functions (Labiano-Fontcuberta et al. 2014). They found that health related QoL total scores were moderately associated with patients' neuropsychological test scores including sustained attention, working memory and information processing, and less with verbal fluency assessment scores. Therefore, the study showed that moderate impairment of many cognitive processes, especially information processing speed, is associated with disease burden. According to studies, the duration of care is influenced by the cognitive and daily activities that the person with MS is able/unable to perform (Finlayson and Cho 2008, Opara et al. 2012). Impairment in cognitive functioning may interfere with daily life and require more assistance from the caregiver. This may reduce the amount of time caregivers dedicate to themselves, which may indirectly lead to depressive symptoms and ultimately a decrease in QoL. The potential for depressive symptoms and reduced QoL highlights the importance of the cognitive symptoms of the disease and the need to develop help to manage them. The effects of impairment in cognitive functions on MS patients and their caregivers are shown in Table 1.

Table 1. The impact of cognitive functions on MS patients and caregivers

Cognitive Domains	**The Impact on MS Patient**	**The Impact on Caregivers**
Memory	Decrease in QoL, unemployment, communication difficulties, depressed mood (Chipchase and Lincoln 2001, Raggi et al. 2016, Halstead et al. 2021)	Decrease in QoL, increase carer strain, decrease amount of time a carer spends alone, challenge coping strategies and feelings, forced to adopt a parenting role (Chipchase and Lincoln 2001, Figved et al 2007, Macías Islas and Ciampi 2019)
Executive Function	Decrease in QoL, cognitive inflexibility, poorer problem-solving skills, depressed mood, difficulties in emotion regulation, dyadic relationship problems (Beatty and Monson 1996, King and Arnett 2005, Chiaravalloti and DeLuca 2008, Drew et al. 2008, Phillips et al. 2014)	Decrease in QoL, increase carer strain (Bayen et al. 2015, Maguire and Maguire 2020)
Information Processing	Decrease in QoL, depressed mood, fatigue, anxiety, work related difficulties, fall frequency, deterioration of family setting (Barker-Collo 2006, Diamond et al. 2008, Sosnoff et al. 2013, Labiano-Fontcuberta et al. 2015)	Decrease in QoL, depressed mood, challenge coping strategies and feelings, forced to adopt a parenting role (Figved et al 2007, Labiano-Fontcuberta et al. 2015, Macías Islas and Ciampi 2019)
Attention	Decrease in QoL, unemployment, work impairment, depressed mood (Glad, Aarseth et al. 2010, Glanz et al. 2010)	Decrease in QoL (Labiano-Fontcuberta et al. 2015)

QoL: Quality of Life

Discussion

It is estimated that 10–20% of MS patients experience more severe cognitive abnormalities, while 40–50% experience mild to moderate cognitive deficits. (Hämäläinen and Rosti-Otajärvi 2016). The studies highlighted the fact that cognitive deficits may develop in any subtype of MS and in the early onset of the disease, even in clinically isolated syndrome (Hämäläinen and Rosti-Otajärvi 2016). It occurs in 20-25% of patients with isolated syndrome, 30-45% of patients with relapsing-remitting MS subtype and 50-75% of patients with secondary progressive MS subtype (Johnen et al. 2017). Studies examining the relationship between cognitive impairment and different MS subtypes have heterogeneous and critically limited results due to their small clinical sample sizes and their focus on RRMS and progressive MS subtypes (Ruano et al. 2017). However, the results from these studies suggest that individuals with progressive MS subtypes such as secondary progressive MS (SPMS) and primary progressive MS (PPMS) suffer from more severe cognitive deficits, especially due to severe cortical atrophy (Vollmer et al. 2016). Thus, while cognitive dysfunction is more severe in the chronic progressive subtypes, cognitive impairment in the clinical isolated form, which is a very early period of the disease, and in the RRMS subtype, which follows a milder course, is not as profound as in other subtypes (Migliore et al. 2017).

The most common cognitive impairments that are observed in MS are memory, executive function, information processing and attention. As studies have shown, memory impairment is one of the most affected cognitive impairments and can manifest itself from the onset of the disease. However, when the neuropsychological profile of MS patients is assessed, impairments in selective sustained, divided attention and information processing, and difficulties with executive functions are among the prominent daily problems. Although the nature of these cognitive dysfunctions in MS is well characterized, studies examining the relationship between reduced cognitive abilities and QoL are limited in number and have yielded conflicting results, as they usually focus on a small number of cognitive functions. Literature has generally focused on various factors affecting QoL in individuals with MS, such as depression, fatigue, sleep quality and disability status, and the effect of cognitive functions has not been sufficiently emphasized. However, despite all these, studies on the effect of cognitive function on QoL in MS patients have started to increase gradually in recent years.

The difficulties experienced by patients in maintaining their daily lives and the decrease in quality of life affect not only the patients but also the caregivers, as it increases the dependence on the carer (Gupta et al. 2012). As expected, caregivers often offer emotional support and arrange social and medical service plans in addition to helping with daily tasks and basic personal hygiene (Opara et al. 2012). Therefore, individuals could endure significant amounts of chronic stress, which could worsen their social lives, health, and general well-being.

Conclusion

The observation of cognitive impairment in addition to well characterized symptoms of MS has been a key indicator of the complex etiology of the disease. The most important major implication of that study is that cognitive impairments in MS patients are as important as other symptoms and greatly affect both the patient and the caregiver. Cognitive dysfunction is important as it manifests itself with decreased satisfaction in work and social life and decreased QoL. In future studies, cognitive impairment in MS patients should be analyzed with a detailed neuropsychological assessment and the contribution of different cognitive functions to caregiver burden should be investigated.

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