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REVIEW

Ataxia in Patients with Multiple Sclerosis: A Brief Review

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Abstract

Ataxia is a significant and often debilitating symptom characterized by the impaired coordination of voluntary muscle movements. It frequently occurs in patients with multiple sclerosis (MS) and profoundly impacts their quality of life. This comprehensive review explores the multifaceted nature of ataxia, including its diverse etiologies such as central nervous system lesions, medication side effects, nutritional deficiencies, and hereditary conditions, as well as its association with various diseases. A detailed examination of ataxia's correlations with neuroanatomy revealed its complex relationship with cerebellar pathology. This emphasized the critical role of the cerebellum and its associated pathways in coordinating voluntary movements. The manifestation of ataxia in MS were examined, highlighting its prevalence, impact on disability and life quality, and the pathological underpinnings within cerebellar structures. Diagnostic approaches, including the International Cooperative Ataxia Rating Scale, Scale for the Assessment and Rating of Ataxia, and nine-hole peg test for assessing upper limb dexterity, were discussed. Furthermore, the treatment strategies were critically reviewed. Although long-term effective options are currently lacking, specific pharmacological agents and rehabilitation techniques have demonstrated some benefits. The review findings indicate that further studies are required to better understand ataxia's dynamics, treatment efficacy, and overall impact on patients with MS. Additionally, there is a pressing need for advancements in management and therapeutic approaches.

Keywords: Ataxia, movement disorders, multiple sclerosis, review

Introduction

Traditionally, movement disorders were considered to be uncommon in multiple sclerosis (MS) (1). However, the true prevalence and incidence of movement disorders in MS remain unknown because most previous reports have been retrospective studies, small case series, or review articles (2,3).

Ataxia, which is characterized by impaired coordination of voluntary muscle movements, may be the main complaint of the patient or one of several accompanying symptoms. It is often caused by cerebellar dysfunction or pathologies in the vestibular or proprioceptive afferent pathways to the cerebellum. However, when considered in more detail, ataxia is a coordination disorder caused by abnormalities in different components of the nervous system, including the brain, spinal cord, peripheral nerves, and nerve roots (4). In addition, hypomyelination with atrophy of the basal ganglia and cerebellum, a recently defined and incompletely understood disorder, has been associated with the development of dystonia, ataxia, rigidity, choreoathetosis and tremor (6). Different types of ataxia can often occur in the same patient due to similar or overlapping causes (5). The following are the possible causes of ataxia: Focal lesions of the central nervous system (such as tumor, stroke, and MS), alcohol, antidepressants, antiepileptic drugs, intoxication, radiation, vitamin B12 deficiency, thyroid diseases, head trauma, celiac disease (gluten ataxia), hereditary disorders (such as Friedreich ataxia, ataxia-telangiectasia, Niemann-Pick disease, and fragile X-related ataxia/tremor syndrome), Arnold-Chiari malformation, Wilson's disease, and metabolic disorders (such as succinic semialdehyde dehydrogenase deficiency).

Localization of Lesion Associated with Ataxia

Establishing a direct relationship between the clinical features of cerebellar pathologies and the cerebellar anatomy can be challenging (7,8). Lesions located in the midline of the cerebellum typically cause gait ataxia, truncal ataxia, and titubation. However, involvement of the paravermian region is associated with speech disturbances. Lesions in the posterior cerebellum

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or the flocculonodular lobe can induce vertigo, ataxia, and eye movement abnormalities. Furthermore, lesions in the ipsilateral cerebellar hemispheres have been associated with limb ataxia (7-10). A crucial aspect of coordinating voluntary movements is the cerebellum's role in integrating sensory pathways. Thus, demyelinating lesions affecting either the central or peripheral sensory pathways, as well as the vestibular system, can lead to sensory ataxia (7,8,11). The clinical findings of ataxia and their correlation with neuroanatomy have been described in Table 1.

Symptoms of Ataxia

Patients may present with different forms of ataxia such as postural/balance disorder, ataxic gait, sensory ataxia, truncal ataxia, limb ataxia, dysdiadokinesia (dysrhythmokinesia), intrinsic tremor, dysmetria, dysarthria, nystagmus, paroxysmal ataxia and dysarthria (PAD), and ataxic hemiparesis. A healthy individual can maintain a stable standing position if their feet are placed less than 12 cm apart. Furthermore, they can remain in a fixed position with their feet together or in tandem for >30 seconds. However, a patient with posture/balance issues cannot maintain these positions. An abnormal posture without motor weakness or involuntary movements may be indicative of cerebellar ataxia or sensory ataxia.

Gait ataxia, which is a lack of coordination in the lower limbs, is caused by cerebellar pathologies or decreased proprioceptive inputs. Individuals may experience a feeling of unsteadiness, a desire to hold on to walls or furniture, or need to keep their feet wide apart, causing an unsteady gait. A worsening in gait disturbance without visual cues (such as walking with eyes closed or in the dark) is indicative of sensory or vestibular ataxia. In patients with cerebellar pathologies, the gait ataxia is similar regardless of visual cues (5).

Patients may present with truncal ataxia, a swaying sensation while sitting or standing (especially with arms extended forward), and titubation. Intentional tremors are caused by an instability in the proximal part of the limb, and its amplitude increases toward the end of a voluntary movement. This is usually evaluated by finger-to-nose and heel-to-shin tests. MS-related tremors have postural and intrinsic components. Furthermore, because these features significantly affect the daily functioning of patients with MS-related tremors, these patients are more likely to be unemployed or retired (12).

Ataxia-associated oculomotor disturbances may present as saccadic dysmetria (eye movements exceeding or lagging behind the target), nystagmus (rapid and involuntary eye movements, especially during lateral gaze) and saccadic intrusions during slow pursuit eye movements (13).

PAD was first proposed by Parker in 1946 (14). It is characterized by short-term stereotypical episodes of speech impairment

Table 1. Correlation between neuroanatomy and the clinical features of ataxia (5)

Neuroanatomy	Function	Ataxia or ataxia-like features arising due to damage of the particular region
Cerebellar hemisphere, including dentate nuclei	Integration of sensory input and motor planning for the coordination of complex tasks	Ipsilateral limb ataxia, dysdiadochokinesia, dysmetria, intention tremor, and scanning speech
Midline cerebellar structures (vermis, fastigial and interposed nuclei, vestibulocerebellum, and paravermis)	Motor execution, rapid and slow eye movements, balance, lower extremity coordination, and vestibular function	Gait ataxia and imbalance, truncal ataxia, dysmetria, ocular findings, head bobbing, and vertigo
Posterior lobe (flocculonodular lobe)	Integration of information from the vestibular nuclei	Nystagmus, postural instability, and gait ataxia
Cerebral cortex (frontal lobe)	Planning and initiation of gait	Frontal ataxia (Bruns apraxia), and magnetic gait (different from ataxic gait). Associated pathology in this region can worsen the ataxia
Brainstem (vestibular nuclei, inferior olivary nuclei, pontine nuclei, and cerebellar peduncles)	Relay of signals in and out of the cerebellum	Ataxia associated with cranial nerve dysfunction and motor-sensory deficits
Spinal cord [cuneate fasciculus, gracile fasciculus, and spinocerebellar tracts (mossy fibers)]	Conduction of sensory pathways	Sensory ataxia
Musculoskeletal system (gluteal muscles)	Stabilization of the weight-bearing hip	Waddling gait rather than ataxia. Associated pathology in this region can worsen the ataxia
Peripheral sensation system and visual system	Proprioception and visual cues, respectively	Sensory ataxia with Romberg sign can worsen cerebellar ataxia
Vestibular system (labyrinth of the inner ear, vestibular nerve, and vestibular nuclei)	Sense of balance and special orientation and maintaining equilibrium	Disequilibrium, loss of balance associated with dizziness and vertigo, tinnitus, hearing impairment, and nystagmus

that may be accompanied by clumsiness in the extremities, feeling of lightheadedness, and unsteady gait. PAD is one of the paroxysmal symptoms in patients with MS. The other symptoms include tonic spasms, trigeminal neuralgia, Lhermitte's sign, paroxysmal pruritus, and other sensory symptoms. These symptoms are usually of sudden onset and short duration (5-15 s), and they may manifest more than one time per hour. In most of the reported cases of PAD, the lesion responsible has been detected in the midbrain, in or near the red nucleus, and in the cerebellum or cerebellar peduncles. Thus, PAD appears to develop due to pathologies of the cerebello-thalamo-cortical pathways (15-18).

Multiple Sclerosis and Ataxia

Ataxia is a common symptom in demyelinating diseases. It manifests in different forms at any time during the disease course in approximately 80% of the patients, and it significantly affects the patients' quality of life (5,19). A recent retrospective analysis of 123 patients with demyelinating disease-related movement disorders identified ataxia as the predominant movement disorder (20). The presence of cerebellar dysfunction significantly exacerbates disability rates, diminishes mobility, and compromises the quality of life (21). Furthermore, the development of cerebellar dysfunction within the first two years after disease onset is associated with a 20% increase in overall future disability (22).

MS-associated cerebellar pathology can arise from alterations in the microstructure of the cerebellar cortex, cerebellar nuclei, and the white matter of the cerebellar peduncles (23-26). Infratentorial lesions have been associated with persistent disability (27). Recent studies have demonstrated that lesions are more prevalent in the pons and cerebellar peduncles than in the other areas among individuals with clinically isolated syndrome (CIS), which often precedes MS (28,29). Furthermore, autopsies have revealed that 38.7% of the cerebellar cortical area can undergo demyelination in patients with MS. In severe cases of MS, >90% of the area may be involved (30). Cerebellar dysfunction may present during acute relapses or, more frequently, as a result of progressive decline in advanced MS (31). The development of cerebellar symptoms in MS is associated with a heightened risk of transitioning to a progressive disease trajectory (32). Furthermore, a reduced cerebellar volume and increased T2 lesion load are associated with greater cognitive and motor challenges, as well as increased clinical disability as determined by the Expanded Disability Status Scale (33). T2 lesions in the middle and superior cerebellar peduncles are commonly found in patients with MS, and they are associated with disease severity and upper limb functionality (31). Furthermore, the cerebellar cortex undergoes demyelination, which becomes more pronounced in individuals with progressive MS (30). However, patients with earlier stages of MS and CIS, exhibit reduced cerebellar white matter and overall brain volume when compared with healthy individuals (34).

Clinical manifestations of cerebellar dysfunction, such as tremors, limb and gait ataxia, and dysarthria, tend to persist following a relapse more frequently than sensory alterations (21,35). This poses a significant challenge to the management and contributes to increased morbidity.

Any injury that interferes with the communication pathways between the cerebellum and higher cortical regions may partially account for the cognitive impairments in patients with MS. These clinically present as executive dysfunction, decline in memory, and language capabilities (36).

Assessment of Ataxia

Clinical scales are essential for the initial assessment and scoring of disease severity, monitoring of progression, and quantification of therapeutic outcomes. Several scales exist for the clinical assessment of cerebellar symptoms. Some scales have been specifically designed and validated for particular cerebellar disorders such as Friedreich ataxia. Other scales effectively identify cerebellar symptoms, irrespective of the underlying causes (37).

Ataxia is a prevalent issue among patients with MS, necessitating the use of appropriate scales to comprehensively evaluate this condition. When evaluating ataxia-related symptoms in patients with MS, the International Cooperative Ataxia Rating Scale (ICARS) and Scale for the Assessment and Rating of Ataxia (SARA) are reliable (37). ICARS rates ataxia-related symptoms on the basis of 19 items under four subscales (posture and gait disturbances, kinetic functions, speech disturbances, and oculomotor disturbances). Although semi-quantitative, ICARS depends on the subjective grading of clinicians (38). Similarly, SARA is a semi-quantitative assessment tool. However, it is much simpler and less time consuming than ICARS (39). The upper limb dexterity and effects of ataxia can be effectively and directly assessed in individuals with MS via the nine-hole peg test (9HPT) (40). This test can accurately differentiate between controls and people with MS with varying degrees of impairment. As part of the MS functional composite, the 9HPT is commonly included with tasks related to walking, visual abilities, and cognition (41).

Treatment of Ataxia

The treatment of ataxia is symptomatic and multidisciplinary. The treatment options include pharmacological drugs, occupational therapy, speech therapy, and rehabilitation. However, despite the numerous treatment-related studies, no single treatment has proved efficacious. In a Cochrane-collaborative systematic review of several randomized controlled trials (including placebo-controlled or drug-controlled trials), the results of 172 patients with ataxia or tremor were included. In this review, the methods of only

ten studies were appropriate. Furthermore, a wide range of therapeutic drugs, including baclofen, pyridoxine, isoniazid, and cannabis, were investigated. The review revealed that no treatment modality, including thalamotomy, deep brain stimulation, physiotherapy and neurorehabilitation, was effective against MS-related ataxia in the long-term. However, the included studies had significant limitations, including their small sample size and inability to quantify treatment benefits (19). In a randomized controlled study conducted in 2020, which included 48 patients with upper extremity ataxia, levetiracetam significantly improved the upper extremity symptoms and dexterity, which was assessed via the 9PHT (38) (Table 2).

In a comprehensive review by Chasiotis et al. (38) in 2023, six non-pharmacological interventional studies on the rehabilitation of cerebellar ataxia in patients with MS were analyzed (39). Of the six studies, three were randomized controlled trials that included two rehabilitation protocols. One protocol was task-oriented training (kinematic exercises involving routine daily life tasks) (40,41), and the other was functional rehabilitation training (42). The remaining three studies were pilot studies with small sample sizes (10-20 participants) that examined the following protocols: combination of NDT-Bobath approach and traditional physiotherapy (43), reeducation using robotic and visual biofeedback (a physiotherapy technique that helps patients control their muscles by visualizing muscle activity in real time) (44), functional rehabilitation (45). The review by Chasiotis et al. (38) revealed that the patient's symptoms and quality of life improve when a combination of different rehabilitation techniques is used to treat ataxia. Furthermore, the symptoms significantly improved when evenly distributed external torso weights and dynamic plasters were used for the treatment of trunk and extremity tremors (46,47).

In conclusion, although ataxia is very common in patients with any stage of MS and throughout the disease course, studies in this field are insufficient. Ataxia typically manifests a few months after a spinal or brainstem/cerebellar relapse. However, they may occasionally be the presenting symptom of a relapse. Failure to recognize MS as a potential cause of new-onset movement disorder can lead to delays in the diagnosis and initiation of disease modifying therapy (47). Therefore, more studies on the frequency, pattern and severity of ataxia, associated factors, MRI features, and treatment modalities of MS-related ataxia are required.

Table 2. Treatment modalities for patients with multiple sclerosis-related ataxia (20)

Treatment modality	Options
Physical	Balance-based torso weighting and task-oriented and core-stability exercises
Pharmacological	Carbamazepine, levetiracetam, phenytoin, acetazolamide, lacosamide, and fingolimod
Surgical	Thalamic deep brain stimulation and thalamotomy

Ethics

Conflict of Interest: The author declare no conflict of interest.

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REFERENCES

1. Mehanna R, Jankovic J. Movement disorders in multiple sclerosis and other demyelinating diseases. J Neurol Sci. 2013;328:1-8.
2. Tranchant C, Bhatia KP, Marsden CD. Movement disorders in multiple sclerosis. Mov Disord. 1995;10:418-423.
3. Oakes PK, Srivatsal SR, Davis MY, Samii A. Movement disorders in multiple sclerosis. Phys Med Rehabil Clin N Am. 2013;24:639-651.
4. Ashizawa T, Xia G. Ataxia. Continuum (Minneap Minn). 2016;22:1208-1226.
5. van der Knaap MS, Linnankivi T, Paetau A, Feigenbaum A, Wakusawa K, Haginoya K, Köhler W, Henneke M, Dinopoulos A, Grattan-Smith P, Brockmann K, Schiffmann R, Blaser S. Hypomyelination with atrophy of the basal ganglia and cerebellum: follow-up and pathology. Neurology. 2007;69:166-171.
6. Mitoma H, Buffo A, Gelfo F, Guell X, Fucà E, Kakei S, Lee J, Manto M, Petrosini L, Shaikh AG, Schmahmann JD. Consensus Paper. Cerebellar Reserve: From Cerebellar Physiology to Cerebellar Disorders. Cerebellum. 2020;19:131-153.
7. Pandolfo M, Manto M. Cerebellar and afferent ataxias. Continuum (Minneap Minn). 2013;19:1312-1343.
8. Li M, Yang MH, Liu Y. [Effects of Chinese herbal medicine Bushen Huoxue Granule on quality of life of patients with Parkinson disease: a randomized, double-blinded and placebo-controlled trial]. Zhong Xi Yi Jie He Xue Bao. 2012;10:310-317.
9. Vidailhet M, Jedynak CP, Pollak P, Agid Y. Pathology of symptomatic tremors. Mov Disord. 1998;13 Suppl 3:49-54.
10. Zhang Q, Zhou X, Li Y, Yang X, Abbasi QH. Clinical Recognition of Sensory Ataxia and Cerebellar Ataxia. Front Hum Neurosci. 2021;15:639871.
11. Koch M, Mostert J, Heersema D, De Keyser J. Tremor in multiple sclerosis. J Neurol. 2007;254:133-145.
12. Lewis RF, Zee DS. Ocular motor disorders associated with cerebellar lesions: pathophysiology and topical localization. Rev Neurol (Paris). 1993;149:665-677.
13. Klaas JP, Burkholder DB, Singer W, Boes CJ. Harry Lee Parker and paroxysmal dysarthria and ataxia. Neurology. 2013;80:311-314.
14. Goodwin SJ, Carpenter AF. Successful treatment of paroxysmal ataxia and dysarthria in multiple sclerosis with levetiracetam. Mult Scler Relat Disord. 2016;10:79-81.
15. Iorio R, Capone F, Plantone D, Batocchi AP. Paroxysmal ataxia and dysarthria in multiple sclerosis. J Clin Neurosci. 2014;21:174-175.
16. Marcel C, Anheim M, Flamand-Rouvière C, Heran F, Masnou P, Boulay C, Mari I, Tranchant C, Roze E. Symptomatic paroxysmal dysarthria-ataxia in demyelinating diseases. J Neurol. 2010;257:1369-1372.
17. Shah S, Klassen BT, Flanagan EP. Teaching Video NeuroImages: Paroxysmal Dysarthria-Ataxia in Multiple Sclerosis. Neurology. 2021;96:e2245-e2246.
18. Mills RJ, Yap L, Young CA. Treatment for ataxia in multiple sclerosis. Cochrane Database Syst Rev. 2007:CD005029.
19. Suarez-Cedeno G, Mehanna R. Movement Disorders in Multiple Sclerosis and Other Demyelinating Diseases: A Retrospective Review From a Tertiary Academic Center. Neurologist. 2021;26:161-166.
20. Parmar K, Stadelmann C, Rocca MA, Langdon D, D'Angelo E, D'Souza M, Burggraaff J, Wegner C, Sastre-Garriga J, Barrantes-Freer A, Dorn J,

Uitdehaag BMJ, Montalban X, Wuerfel J, Enzinger C, Rovira A, Tintore M, Filippi M, Kappos L, Sprenger T; MAGNIMS study group. The role of the cerebellum in multiple sclerosis-150 years after Charcot. Neurosci Biobehav Rev. 2018;89:85-98.

21. Le M, Malpas C, Sharmin S, Horáková D, Havrdova E, Trojano M, Izquierdo G, Eichau S, Ozakbas S, Lugaresi A, Prat A, Girard M, Duquette P, Larochelle C, Alroughani R, Bergamaschi R, Sola P, Ferraro D, Grammond P, Grand' Maison F, Terzi M, Boz C, Hupperts R, Butzkueven H, Pucci E, Granella F, Van Pesch V, Soysal A, Yamout BI, Lechner-Scott J, Spitaleri D, Ampapa R, Turkoglu R, Iuliano G, Ramo-Tello C, Sanchez-Menoyo JL, Sidhom Y, Gouider R, Shaygannejad V, Prevost J, Altintas A, Fragoso YD, McCombe PA, Petersen T, Slee M, Barnett MH, Vucic S, Van Der Walt A, Kalincik T. Disability outcomes of early cerebellar and brainstem symptoms in multiple sclerosis. Mult Scler. 2021;27:755-766.
22. Cendelin J, Buffo A, Hirai H, Magrassi L, Mitoma H, Sherrard R, Vozeh F, Manto M. Task Force Paper On Cerebellar Transplantation: Are We Ready to Treat Cerebellar Disorders with Cell Therapy? Cerebellum. 2019;18:575-592.
23. Gilmore CP, Donaldson I, Bö L, Owens T, Lowe J, Evangelou N. Regional variations in the extent and pattern of grey matter demyelination in multiple sclerosis: a comparison between the cerebral cortex, cerebellar cortex, deep grey matter nuclei and the spinal cord. J Neurol Neurosurg Psychiatry. 2009;80:182-187.
24. Preziosa P, Rocca MA, Mesaros S, Pagani E, Drulovic J, Stosic-Opincal T, Dackovic J, Copetti M, Caputo D, Filippi M. Relationship between damage to the cerebellar peduncles and clinical disability in multiple sclerosis. Radiology. 2014;271:822-830.
25. Prosperini L, Sbardella E, Raz E, Cercignani M, Tona F, Bozzali M, Petsas N, Pozzilli C, Pantano P. Multiple sclerosis: white and gray matter damage associated with balance deficit detected at static posturography. Radiology. 2013;268:181-189.
26. Minneboo A, Barkhof F, Polman CH, Uitdehaag BM, Knol DL, Castelijns JA. Infratentorial lesions predict long-term disability in patients with initial findings suggestive of multiple sclerosis. Arch Neurol. 2004;61:217-221.
27. Giorgio A, Battaglini M, Rocca MA, De Leucio A, Absinta M, van Schijndel R, Rovira A, Tintoré M, Chard D, Ciccarelli O, Enzinger C, Gasperini C, Frederiksen J, Filippi M, Barkhof F, De Stefano N; MAGNIMS Study Group. Location of brain lesions predicts conversion of clinically isolated syndromes to multiple sclerosis. Neurology. 2013;80:234-241.
28. Droby A, Fleischer V, Carnini M, Zimmermann H, Siffrin V, Gawehn J, Erb M, Hildebrandt A, Baier B, Zipp F. The impact of isolated lesions on white-matter fiber tracts in multiple sclerosis patients. Neuroimage Clin. 2015;8:110-116.
29. Kutzelnigg A, Faber-Rod JC, Bauer J, Lucchinetti CF, Sorensen PS, Laursen H, Stadelmann C, Brück W, Rauschka H, Schmidbauer M, Lassmann H. Widespread demyelination in the cerebellar cortex in multiple sclerosis. Brain Pathol. 2007;17:38-44.
30. Wilkins A. Cerebellar Dysfunction in Multiple Sclerosis. Front Neurol. 2017;8:312.
31. Albert M, Barrantes-Freer A, Lohrberg M, Antel JP, Prineas JW, Palkovits M, Wolff JR, Brück W, Stadelmann C. Synaptic pathology in the cerebellar dentate nucleus in chronic multiple sclerosis. Brain Pathol. 2017;27:737-747.
32. D'Ambrosio A, Pagani E, Riccitelli GC, Colombo B, Rodegher M, Falini A, Comi G, Filippi M, Rocca MA. Cerebellar contribution to motor and cognitive performance in multiple sclerosis: An MRI sub-regional volumetric analysis. Mult Scler. 2017;23:1194-1203.
33. Ramasamy DP, Benedict RH, Cox JL, Fritz D, Abdelrahman N, Hussein S, Minagar A, Dwyer MG, Zivadinov R. Extent of cerebellum, subcortical and cortical atrophy in patients with MS: a case-control study. J Neurol Sci. 2009;282:47-54.
34. Nixon PD. The role of the cerebellum in preparing responses to predictable sensory events. Cerebellum. 2003;2:114-122.
35. Schoonheim MM, Douw L, Broeders TA, Eijlers AJ, Meijer KA, Geurts JJ. The cerebellum and its network: Disrupted static and dynamic functional connectivity patterns and cognitive impairment in multiple sclerosis. Mult Scler. 2021;27:2031-2039.
36. Bürk K, Sival DA. Scales for the clinical evaluation of cerebellar disorders. Handb Clin Neurol. 2018;154:329-339.
37. Solaro C, de Sire A, Messmer Uccelli M, Mueller M, Bergamaschi R, Gasperini C, Restivo DA, Stabile MR, Patti F. Efficacy of levetiracetam on upper limb movement in multiple sclerosis patients with cerebellar signs: a multicenter double-blind, placebo-controlled, crossover study. Eur J Neurol. 2020;27:2209-2216.
38. Chasiotis AK, Kitsos DK, Stavrogianni K, Giannopapas V, Papadopoulou M, Zompola C, Paraskevas GP, Bakalidou D, Giannopoulos S. Rehabilitation on cerebellar ataxic patients with multiple sclerosis: A systematic review. J Neurosci Res. 2023;101:1773-1780.
39. Ali AS, Darwish MH, Shalaby NM, Abbas RL, Soubhy HZ. Efficacy of core stability versus task oriented trainings on balance in ataxic persons with multiple sclerosis. A single blinded randomized controlled trial. Mult Scler Relat Disord. 2021;50:102866.
40. Salcı Y, Fil A, Armutlu K, Yildiz FG, Kurne A, Aksoy S, Nurlu G, Karabudak R. Effects of different exercise modalities on ataxia in multiple sclerosis patients: a randomized controlled study. Disabil Rehabil. 2017;39:2626-2632.
41. Scheidler AM, Kinnett-Hopkins D, Learmonth YC, Motl R, López-Ortiz C. Targeted ballet program mitigates ataxia and improves balance in females with mild-to-moderate multiple sclerosis. PLoS One. 2018;13:e0205382.
42. Keser I, Kirdi N, Meric A, Kurne AT, Karabudak R. Comparing routine neurorehabilitation program with trunk exercises based on Bobath concept in multiple sclerosis: pilot study. J Rehabil Res Dev. 2013;50:133-140.
43. Klatt BN, Sparto PJ, Terhorst L, Winser S, Heyman R, Whitney SL. Relationship between subjective visual vertical and balance in individuals with multiple sclerosis. Physiother Res Int. 2019;24:e1757.
44. Rahimibarghani S, Emami-Razavi SZ, Naser Moghadasi A, Azadvari M, Shojaee Fard M, Rahimi-Dehgolan S. Quantitative Changes in Gait Parameters after Cycling among Multiple Sclerosis Patients with Ataxia: A Pilot Study. jmr. 2022;16:355-363.
45. Ayvat E, Kılınç ÖO, Ayvat F, Sütçü G, Kılınç M, Aksoy S, Yıldırım SA. The use of Goal Attainment Scaling (GAS) in the rehabilitation of ataxic patients. Neurol Sci. 2018;39:893-901.
46. Widener GL, Conley N, Whiteford S, Gee J, Harrell A, Gibson-Horn C, Block V, Allen DD. Changes in standing stability with balance-based torso-weighting with cerebellar ataxia: A pilot study. Physiother Res Int. 2020;25:e1814.
47. Abboud H, Yu XX, Knusel K, Fernandez HH, Cohen JA. Movement disorders in early MS and related diseases: A prospective observational study. Neurol Clin Pract. 2019;9:24-31.

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REVIEW

Effects of Motor Imagery Training on Health-related Quality of Life in Persons with Multiple Sclerosis: A Narrative Review

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Abstract

Multiple sclerosis (MS) is a chronic autoimmune disorder that impacts the central nervous system. It typically develops during young adulthood, substantially impacting the health-related quality of life (HRQoL) through physical, cognitive, and psychosocial dysfunction. Recent breakthroughs in medical and rehabilitative approaches stress the need to enhance HRQoL for MS patients. Motor imagery (MI) training, involving the mental rehearsal of physical movements without actual execution, has emerged as a promising rehabilitation technique. This method activates neural circuits analogous to those during physical movement and improves motor function and psychological well-being in diverse neurological conditions, including MS. This narrative review synthesizes existing research on the effects of MI training on HRQoL in MS patients. Studies consistently report enhancements in motor function, including improved walking and reduced symptoms of fatigue and depression following MI interventions. Despite differing protocols and methodologies, the findings collectively suggest that MI training can enhance HRQoL in MS patients. Implementing MI training presents difficulties, including standardizing protocols, ensuring patient adherence, and addressing cognitive impairments influencing training effectiveness. In conclusion, MI training exhibits potential to enhance HRQoL in MS patients by addressing both physical and psychological aspects of the disease, thereby boosting overall well-being and functional independence.

Keywords: Multiple sclerosis, motor imagery, quality of life, rehabilitation, walking

Introduction

Multiple sclerosis (MS) is a chronic autoimmune neurological disorder characterized by inflammatory demyelination and axonal damage (1). It is typically diagnosed between the ages of 20 and 30, when individuals are at their most active in their social and professional lives (1). An approximated 2.9 million individuals worldwide are believed to be living with MS, as indicated by recent epidemiological studies (2).

Since MS can affect various regions of the central nervous system, it causes several symptoms and signs, including motor, sensory, visual, and autonomic disorders, impairing physical and cognitive function and adversely influencing employment (1,3,4). These negative consequences in MS patients result in activity limitations, participation restrictions, and disability. Additionally, MS is a chronic disease that frequently features relapses and unpredictable progression. It substantially impairs the psychological, social, and economic status of individuals due to its extensive array of impairments and limitations. These factors raise concerns regarding the right to a healthy life, which is considered one of the most fundamental human rights. The primary objective of treatment and management in MS, as with all diseases, should be to enhance the quality of life for individuals.

Previous research on the impact of MS was mainly focused on impairment and disability (5). However, in 1992, Rudick et al. (6) conducted a pioneering study that investigated the health-related quality of life (HRQoL) in MS patients. This study contrasted patients with MS, inflammatory bowel disease, and rheumatoid arthritis and discovered that MS patients exhibited the lowest HRQoL. Similarly, in 1996, Petajan et al. (7) conducted an innovative randomized controlled trial that studied the effects of exercise in MS patients. This study indicated that aerobic exercise training had a beneficial effect on physical fitness and quality of life. Over the past 30 years, there have been numerous positive advancements in the medical and

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rehabilitation fields related to MS. As the importance of HRQoL has increased, its assessment and use as an outcome measure have become more significant in clinical research, practice, and health policy decision-making.

Overview of Motor Imagery Training

Motor imagery (MI) training entails the mental rehearsal of physical movements without performing actual movements (8). This technique engages neural circuits similar to those that are activated during the physical execution of movements. MI training has been employed in diverse neurological rehabilitation settings to enhance various functions, primarily physical function, with promising results (9-11). MI training is a low-risk, non-invasive intervention that can be incorporated into rehabilitation programs to address the physical and psycho-socioeconomic challenges faced by MS patients (11-13).

The effectiveness of MI training is based on its ability to trigger neural plasticity. Neuroplasticity describes the brain's ability to reorganize by establishing new neural connections and modifying cortical organization (14). This is essential in MS, where demyelination and axonal damage impair normal neural communication (15). MI training stimulates brain regions involved in both motor processes, thereby facilitating neural adaptation and compensatory mechanisms. Studies using neuroimaging techniques, including functional magnetic resonance imaging and positron emission tomography, as well as transcranial magnetic stimulation studies, have demonstrated heightened activity in the motor and premotor regions of the brain during MI (16-19). This heightened activity is comparable to that observed during actual movement, indicating that MI training can enhance motor planning and execution pathways.

Motor function enhancement is one of the primary objectives of MI training in MS patients. Mobility and overall independence are significantly influenced by motor impairments associated with MS, including muscle weakness, spasticity, and coordination difficulties. Several studies have demonstrated that MI training can lead to notable improvements in physical function, particularly in walking ability in MS patients (20-23). These studies documented increased walking endurance, walking speed, and resolution of self-reported walking difficulties. Additionally, Kahraman et al. (21) reported that MI training is also effective in improving dynamic and static balance, as well as balance confidence.

Research has demonstrated that symptoms such as depression, fatigue, cognitive disorders, and sleep disturbances are prevalent and can exert detrimental effects on daily life as well as social and professional activities (24,25). Psychosocial well-being can also be improved through MI training. Numerous studies have demonstrated that MI training substantially improves cognitive functions, depression, anxiety, and fatigue symptoms (20-23).

Walking speed and fatigue were the most improved outcome measures, as reported by four studies (20-23), followed by walking endurance (20,22,23) and self-reported walking difficulties (20-22) as reported by three studies (Figure 1).

Outcome Measures to Assess Health-related Quality of Life in the Reviewed Studies

Several questionnaires, including the Multiple Sclerosis International Quality of Life Questionnaire (MusiQoL), the Multiple Sclerosis Impact Scale-29 (MSIS-29), the Short Form Health Survey-36 (SF-36), and the EuroQol 5-Dimension (EQ-5D) questionnaire, have been employed across the reviewed studies when evaluating HRQoL in MS patients. It is crucial to consider the strengths and limitations of each of these instruments when interpreting the results and selecting suitable measures for future research.

MusiQoL is explicitly designed for MS patients, capturing the distinctive challenges and experiences associated with the disease (26). This specificity increases its relevance and sensitivity to alterations in HRQoL in MS patients. It offers a comprehensive evaluation of HRQoL, encompassing a wide variety of life domains, such as psychological well-being, relationships, and daily activities. The detailed nature of MusiQoL can be tedious for certain patients, particularly those with cognitive impairments or severe disabilities, which may impact response rates and data accuracy. It may not be appropriate for comparisons with the general population norms or individuals with other chronic conditions due to its MS-specificity.

Like MusiQoL, MSIS-29 is designed for MS patients; however, it is more concise and uncomplicated, which facilitates completion by the participants (27). It specifically assesses the physical and psychological impact of MS, which are essential components of HRQoL in this demographic. MSIS-29 may not adequately address other aspects of HRQoL, such as social relationships or economic factors, despite its success in capturing physical and psychological effects. Additionally, a study indicated that MSIS-29 may be restricted in its ability to evaluate alterations associated with disease-modifying therapies in patients with minimal disability (28).

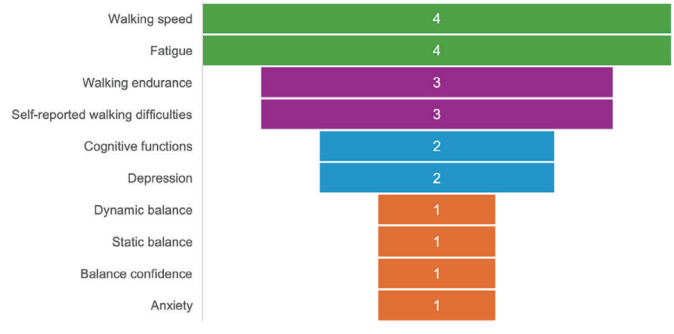


Figure 1. Number of studies reporting substantial improvement in different study outcome measures following motor imagery training

Table 1. Details of studies exploring the effects of motor imagery training on HRQoL in MS patients

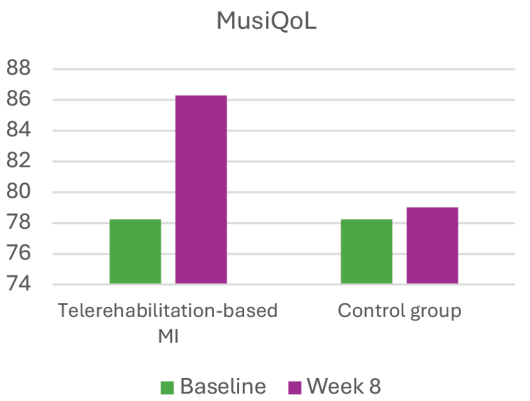
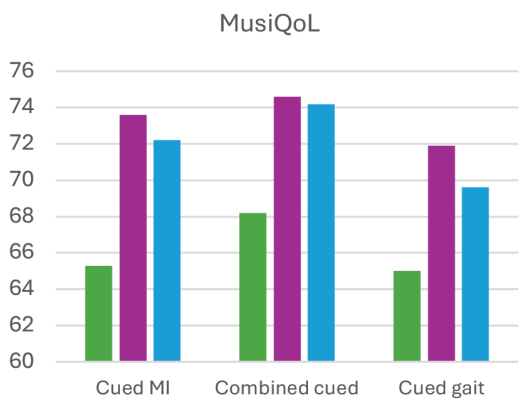
Study	Groups (number of participants) and EDSS score	Interventions	Outcome measure for HRQoL	Key findings on HRQoL	Visual representation of key findings
Kahraman et al. (21)	Telerehabilitation-based MI (n=20): EDSS, median (IQR) = 1 (0-1.75) Control group (n=15): EDSS, median (IQR) = 2 (0-2.5) Healthy controls (n=20)	Telerehabilitation-based MI: 2 times/week 20-30 minutes 8 weeks 16 sessions in total Control group: No intervention	MusiQoL	Baseline (pre-intervention): Telerehabilitation-based MI = 78.22 (70.36, 84.07) Control group = 78.22 (72.58, 84.67) After 8 weeks (post-intervention): Telerehabilitation-based MI = 86.29 (82.25, 94.35), change from baseline = 8.87 (0, 20.16); p=0.002* Control group = 79.03 (66.73, 90.92), change from baseline = -1.21 (-7.66, 7.46); p=0.802	
Seebacher et al. (23)	Cued MI (n=44): EDSS, median (IQR) = 2.5 (2.0-4.0) Combined cued MI and cued gait training (n=44): EDSS, median (IQR) = 3.0 (2.5-4.0) Cued gait training (n=44): EDSS, median (IQR) = 3.0 (2.0-4.0)	For all groups: 4 times/week 30 minutes, 4 weeks 16 sessions in total	MusiQoL	Baseline (pre-intervention): Cued MI = 65.3 (59.4-81.4) Combined cued MI and cued gait training = 68.2 (61.5-73.3) Cued gait training = 65.0 (57.2-69.6) Week 4 (post-intervention): Cued MI = 73.6 (67.0-99.6), change from baseline = 9.1 (0.8-18.2); p<0.001* Combined cued MI and cued gait training = 74.6 (67.7-82.1), change from baseline = 6.7 (-1.4 to 15.4); p=0.003* Cued gait training = 71.9 (65.2-77.9), change from baseline = 8.3 (2.3-4.9); p<0.001* Week 13 (follow-up): Cued MI = 72.2 (58.6-96.6), change from baseline = 5.9 (-4.0-15.5); p=0.027* Combined cued MI and cued gait training = 74.2 (64.0-79.0), change from baseline = 6.4 (-1.5 to 13.2); p=0.036* Cued gait training = 69.6 (62.5-78.2), change from baseline = 4.5 (1.8.0 to 12.4); p=0.001*	

Table 1. Continued

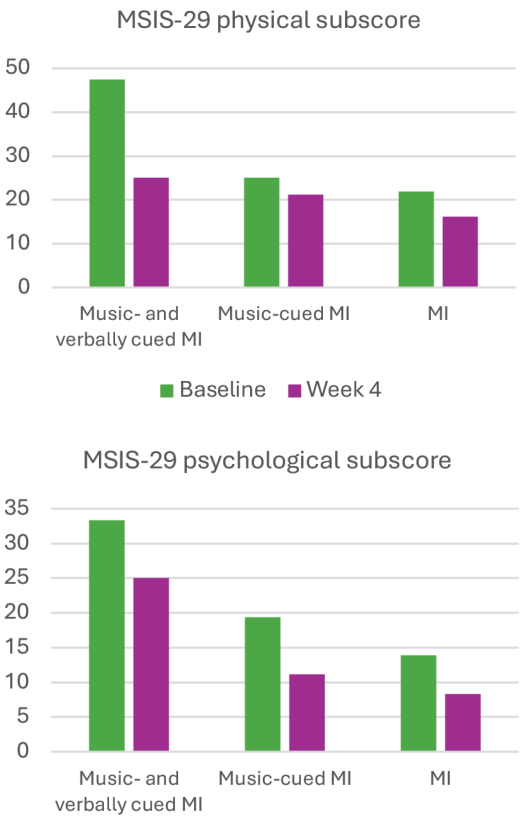
Study	Groups (number of participants) and EDSS score	Interventions	Outcome measure for HRQoL	Key findings on HRQoL	Visual representation of key findings
Seebacher et al. (20)	Music- and verbally cued MI (n=19): EDSS, median (range) = 3.0 (1.5-4.5) Music-cued MI (n=20): EDSS, median (range) = 2.5 (1.5-4.5) MI (n=20): EDSS, median (range) = 2.5 (1.5-4.5)	For all groups: 6 times/week 17 minutes, 4 weeks 24 sessions in total	MSIS-29 (physical and psychological subscore)	Baseline (pre-intervention) for MSIS-29 physical subscore: Music- and verbally cued MI = 47.5 (12.5, 76.2) Music-cued MI = 25 (6.2, 56.2) MI = 21.9 (3.7, 63.7) Week 4 (post-intervention) for MSIS-29 physical subscore: Music- and verbally cued MI = 25.0 (5.0, 61.2), change from baseline = -15.0 (-38.7, -1.2)*, clinically significant improvement: n=15 (78.9%)* Music-cued MI = 21.2 (2.5, 37.5), change from baseline = -7.5 (-28.7, 8.7), clinically significant improvement: n=10 (50%) MI = 16.2 (2.5, 51.2), change from baseline = -3.1 (-41.2, 8.7), clinically significant improvement: n=7 (35%) Baseline (pre-intervention) for MSIS-29 psychological subscore: Music- and verbally cued MI = 33.3 (2.8, 66.7) Music-cued MI = 19.4 (0.0, 47.2) MI = 13.9 (0.0, 66.7) Week 4 (post-intervention) for MSIS-29 psychological subscore: Music- and verbally cued MI = 25.0 (2.8, 50.0), change from baseline = -11.1 (-50.0, 16.7), clinically significant improvement: n=12 (63.2%) Music-cued MI = 11.1 (0.0, 36.1), change from baseline = -2.3 (-19.4, 13.9), clinically significant improvement: n=9 (45%) MI = 8.3 (0.0, 52.8), change from baseline = -1.4 (-38.9, 19.4), clinically significant improvement: n=8 (40%)	

Table 1. Continued

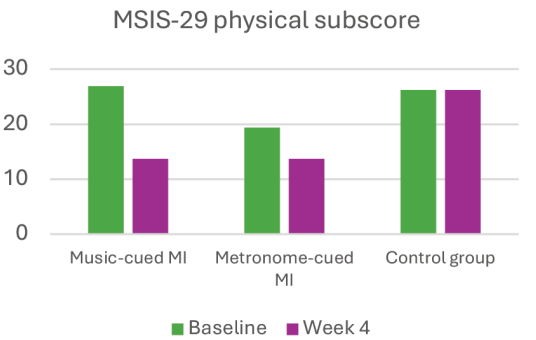
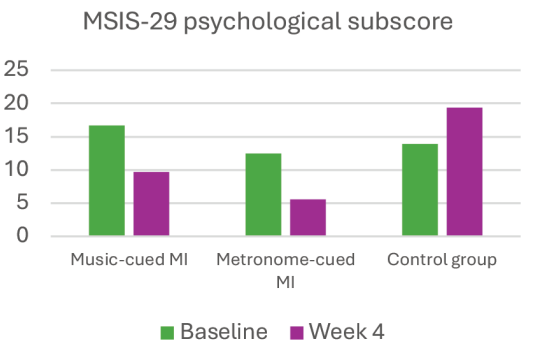
Study	Groups (number of participants) and EDSS score	Interventions	Outcome measure for HRQoL	Key findings on HRQoL	Visual representation of key findings
Seebacher et al. (22)	Music-cued MI (n=34): EDSS, median (range) = 2.0 (1.5-4.5) Metronome-cued MI (n=34): EDSS, median (range) = 2.0 (1.5-4.5) Control group (n=33): EDSS, median (range) = 2.0 (1.5-4.5)	For intervention groups: 6 times/week 17 minutes, 4 weeks 24 sessions in total Control group: No intervention	MSIS-29 (physical and psychological subscore) SF-36 (physical and mental subscore) EQ-5D-3L (index value and VAS)	Baseline (pre-intervention) for MSIS-29 physical subscore: Music-cued MI = 26.9 (2.5-53.8) Metronome-cued MI = 19.4 (1.2-81.2) Control group = 26.2 (2.5-52.5) Week 4 (post-intervention) for MSIS-29 physical subscore: Music-cued MI = 13.7 (0-51.2), change from baseline = -6.9 (-36.2-7.5)*, clinically significant improvement: n=17 (50%) Metronome-cued MI = 13.7 (0-63.7), change from baseline = -5 (-42.5-6.2)*, clinically significant improvement: n=14 (41.2%) Control group = 26.2 (1.2-75), change from baseline = 1.2 (-22.5-48.7), clinically significant improvement: n=7 (21.2%)	
				Baseline (pre-intervention) for MSIS-29 psychological subscore: Music-cued MI = 16.7 (0-55.6) Metronome-cued MI = 12.5 (0-58.3) Control group = 13.9 (0-61.1) Week 4 (post-intervention) MSIS-29 psychological subscore: Music-cued MI = 9.7 (0-41.7), change from baseline = -6.9 (-41.7 to 8.3)*, clinically significant improvement: n=19 (55.9%)* Metronome-cued MI = 5.6 (0-63.9), change from baseline = -2.8 (-27.8 to 5.6)*, clinically significant improvement: n=10 (29.4%) Control group = 19.4 (0-63.9), change from baseline = 2.8 (-13.9 to 38.9), clinically significant improvement: n=4 (12.1%)	

Table 1. Continued

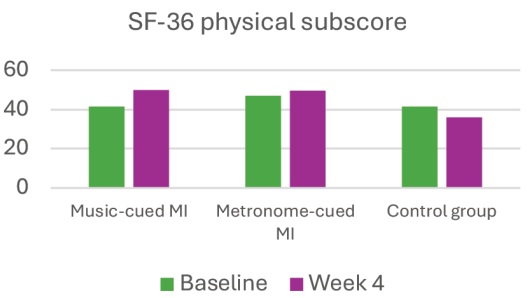
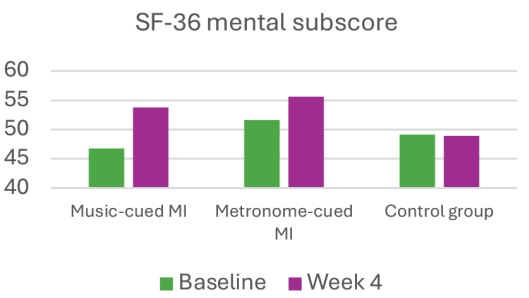
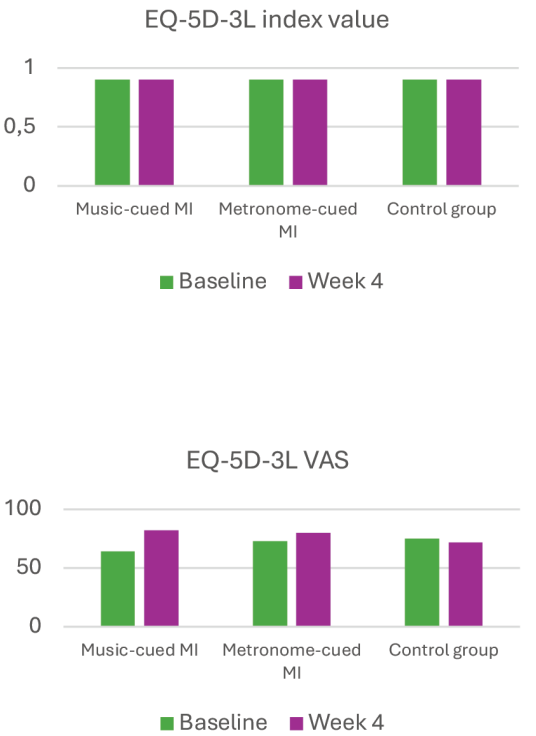
Study	Groups (number of participants) and EDSS score	Interventions	Outcome measure for HRQoL	Key findings on HRQoL	Visual representation of key findings
Seebacher et al. (22)	Music-cued MI (n=34): EDSS, median (range) = 2.0 (1.5-4.5) Metronome-cued MI (n=34): EDSS, median (range) = 2.0 (1.5-4.5) Control group (n=33): EDSS, median (range) = 2.0 (1.5-4.5)	For intervention groups: 6 times/week 17 minutes, 4 weeks 24 sessions in total Control group: No intervention	MSIS-29 (physical and psychological subscore) SF-36 (physical and mental subscore) EQ-5D-3L (index value and VAS)	Baseline (pre-intervention) for SF-36 physical subscore: Music-cued MI = 41.4 (19.1-62.7) Metronome-cued MI = 47.1 (18.5-66) Control group = 41.6 (24.5-59.6) Week 4 (post-intervention) for SF-36 physical subscore: Music-cued MI = 50 (27.7-63.1), change from baseline = 2.7 (-4.8 to 22.8)*, clinically significant improvement: n=15 (44.1%)* Metronome-cued MI = 49.7 (16.6-61.8), change from baseline = 2.3 (-12 to 16.6)*, clinically significant improvement: n=12 (31.3%)* Control group = 35.9 (24.8-58.1), change from baseline = -2.5 (-24.5 to 6.4), clinically significant improvement: 2/33 (6.1%)	
				Baseline (pre-intervention) for SF-36 mental subscore: Music-cued MI = 46.8 (21.5-62.4) Metronome-cued MI = 51.6 (12.2-65.5) Control group = 49.1 (21.8-63.9) Week 4 (post-intervention) for SF-36 mental subscore: Music-cued MI = 53.8 (25.2-64.3), change from baseline = 2.4 (-15.1 to 22.9)*, clinically significant improvement: n=13 (38.3%) Metronome-cued MI = 55.6 (25.2-65.6), change from baseline = 2 (-14 to 28.1)*, clinically significant improvement: 11/34 (32.4%) Control group = 48.9 (23.4-62.7), change from baseline = -0.3 (-14.9 to 14.2), clinically significant improvement: n=4 (12.1%)	

Table 1. Continued

Study	Groups (number of participants) and EDSS score	Interventions	Outcome measure for HRQoL	Key findings on HRQoL	Visual representation of key findings
Seebacher et al. (22)	Music-cued MI (n=34): EDSS, median (range) = 2.0 (1.5-4.5) Metronome-cued MI (n=34): EDSS, median (range) = 2.0 (1.5-4.5) Control group (n=33): EDSS, median (range) = 2.0 (1.5-4.5)	For intervention groups: 6 times/week 17 minutes, 4 weeks 24 sessions in total Control group: No intervention	MSIS-29 (physical and psychological subscore) SF-36 (physical and mental subscore) EQ-5D-3L (index value and VAS)	Baseline (pre-intervention) for EQ-5D-3L index value: Music-cued MI = 0.9 (0.6-1.0) Metronome-cued MI = 0.9 (0.1-1.0) Control group = 0.9 (0.3-1.0) Week 4 (post-intervention) for EQ-5D-3L index value: Music-cued MI = 0.9 (0.7-1), change from baseline = 0 (-0.1 to 0.4) Metronome-cued MI = 0.9 (0.2-1), change from baseline 0 (0.1 to 0.2) Control group = 0.9 (0.3-1), change from baseline = 0 (-0.6 to 0.5) Baseline (pre-intervention) for EQ-5D-3L VAS: Music-cued MI = 64 (30-100) Metronome-cued MI = 73 (24-100) Control group = 75 (30-95) Week 4 (post-intervention) for EQ-5D-3L VAS: Music-cued MI = 82 (40-100), change from baseline = 9 (-10 to 33)*, clinically significant improvement: n=19 (55.9%)* Metronome-cued MI = 80 (35-100), change from baseline = 5 (-8 to 51)*, clinically significant improvement: 11/34 (32.4%) Control group = 72 (30-97), change from baseline = 0 (-15 to 35), clinically significant improvement: n=6 (18.2%)	

*p<0.05, EDSS: Expanded disability status scale, IQR: Interquartile range, HRQoL: Health-related quality of life, MS: Multiple sclerosis, MI: Motor imagery, MusiQoL: Multiple sclerosis international quality of life, MSIS-29: Multiple sclerosis impact scale-29, SF-36: Short Form-36, EQ-5D-3L: EuroQol-5D-3L Questionnaire, VAS: Visual analog scale

SF-36 is a HRQoL instrument that is extensively used across different populations and conditions, including MS (29,30). Its comprehensive validation facilitates reliable comparisons with the general population data and other disease groups. It assesses multiple dimensions of health, including physical functioning, pain, general health perceptions, and mental health, providing a comprehensive assessment of HRQoL. SF-36 may conceivably underestimate the impact of MS on certain aspects of life by overlooking some MS-specific issues as a generic measure. While its broad applicability and exhaustive nature render it valuable, the SF-36 scoring process can be complex. The calculation of its eight subscales and two summary measures (physical and mental health) is particularly complex, necessitating meticulous interpretation to prevent errors or inconsistencies (31).

EQ-5D is a simple instrument that can be rapidly administered, making it suitable for use in large studies or clinical settings where time is limited (32). It offers a single utility score that can be employed in cost-effectiveness analyses, which is valuable for health economics and policy decision-making. The simplicity of EQ-5D comes at the expense of depth. It covers only five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), which may result in the neglect of other critical components of HRQoL in MS patients (33).

Each of these HRQoL questionnaires has its own unique set of strengths and limitations, rendering them appropriate for different research or clinical contexts. The selection of the instrument, the characteristics of the MS population being evaluated, and the HRQoL aspects that are most pertinent to the intervention or outcome under investigation should be determined by the specific objectives of the study. To achieve a thorough understanding of the influence of MI training on the HRQoL in MS patients, it would be beneficial to integrate disease-specific instruments with generic measures. This method strikes a balance between the comprehensive insights offered by specialized instruments and the more general, analogous data from general assessments.

Health-related Quality of Life Improvements After Motor Imagery Training

Quality of life is a multifaceted concept that encompasses physical health, psychological state, social relationships, and environmental factors (34). Enhanced physical and cognitive functions, along with improved psychosocial well-being, contribute to a more holistic sense of health and fulfillment. MI training has been shown to significantly improve HRQoL in individuals with MS, despite the fact that HRQoL has not been the primary outcome measure in previous studies (20-23).

Kahraman et al. (21) employed the MusiQoL scale to evaluate HRQoL following an 8-week telerehabilitation-based MI program for MS patients. Their study demonstrated that this intervention significantly improved HRQoL, with a large effect size ($p=0.002$, Cohen's $d=1.916$). Similarly, Seebacher et al. (23) used the MusiQoL as a secondary outcome measure and reported that cued MI training significantly enhanced MusiQoL scores at the fourth week ($p<0.001$) and follow-up (week 13) ($p=0.027$) compared to the baseline. Additionally, they demonstrated that combining cued MI with cued gait training also improved MusiQoL scores at the fourth week ($p=0.003$) and week 13 ($p=0.036$) compared to the baseline.

In a 2019 study, Seebacher et al. (20) used the MSIS-29 to evaluate HRQoL while investigating the effects of a four-week program that involved music and verbally cued MI, music-cued MI, or MI alone in MS patients. They discovered that 78.9% of participants in the music and verbally cued MI group exhibited clinically significant improvements in the MSIS-29 physical subscore ($p<0.05$), despite not demonstrating improvement in the total or psychological subscores. No significant improvements were noted in the other groups in HRQoL.

In a separate 2017 study, Seebacher et al. (22) examined the impact of 4-week music-cued MI and metronome-cued MI on HRQoL in persons with MS, using diverse tools including the MSIS-29, SF-36, and EQ-5D-3L. They revealed that both music-cued and metronome-cued MI significantly enhanced MSIS-29 physical and psychological subscores, SF-36 physical and mental subscores, and EQ-5D-3L visual analog scores ($p<0.05$).

MI training methods and treatments differ across studies. The therapy sessions are scheduled to last between 17 and 30 minutes, with a frequency of 2 to 6 week. The total treatment duration is 4 to 8 weeks, resulting in 16 to 24 sessions overall. Table 1 contains the specifics of the studies that investigated the impact of MI training on MS patients' HRQoL.

Clinical Implications

These results underscore the potential of MI training as a non-invasive, cost-effective intervention that can improve HRQoL in MS patients (11). MI training can contribute to a more comprehensive approach to MS management by improving physical and cognitive functions, as well as social and emotional well-being (Figure 1). Clinicians should contemplate incorporating MI training into rehabilitation programs to aid MS patients in achieving better overall outcomes.

Possible Challenges

Despite its benefits, the implementation of MI training in clinical practice faces numerous challenges. The necessity of standardized protocols for ensuring consistent and replicable results is underscored by the variation in outcome measures, duration, and delivery modalities of MI across studies. Additionally, patient adherence and engagement in MI training programs can vary, potentially impacting the efficacy of the intervention.

Ensuring access to technology and the provision of adequate training for both patients and healthcare providers are critical factors in the successful incorporation of MI training into routine care. Moreover, cognitive impairments, disability, and cognitive fatigue are known to negatively influence MI ability in MS patients (13). The effectiveness of MI training may also be influenced by other factors, including the phenotype of MS, anxiety, and depression (13). It is essential to resolve these issues by implementing appropriate precautions and support mechanisms to increase patient participation and maximize the benefits of the intervention.

Future Directions

To further substantiate the efficacy of MI training in enhancing the HRQoL of individuals with MS, future research should prioritize large-scale, randomized controlled trials. Investigating the long-term consequences and identifying optimal training protocols will be essential for optimizing the benefits of this intervention on HRQoL.

Developing standardized guidelines and protocols for MI training in MS is essential. These guidelines should specify training frequency, duration, and intensity to ensure consistency and effectiveness across various clinical settings, ultimately enhancing HRQoL. Furthermore, integrating technological advancements such as virtual reality, biofeedback, and telerehabilitation may enhance the delivery and engagement of MI training. These innovations can increase the accessibility and efficacy of the training, thereby potentially yielding more substantial enhancements in HRQoL for MS patients.

It is imperative to recognize that most participants exhibited minimal levels of disability in the context of the reviewed studies. This characteristic may restrict the generalizability of the results to the broader population of MS patients, particularly those with higher disability levels. Future research should endeavor to involve a more diverse range of participants, particularly those with moderate to severe disability. Expanding the participant pool to encompass individuals with differing degrees of disability would also enable a more detailed exploration of the potential need for MI training to be customized to address the specific needs of those with higher disability levels. Additionally, the effectiveness of MI training in improving HRQoL for those with more severe disabilities is a field that remains largely unexplored. Addressing this gap could result in more inclusive and comprehensive guidelines that accommodate the complete spectrum of disability in MS patients, thereby improving the overall outcomes for this population.

Conclusion

MI training is a promising intervention for enhancing the HRQoL in MS patients. This method addresses multiple aspects of MS by improving physical, cognitive, and psychosocial functions. Further research and clinical implementation of MI training are necessary, as the significance of HRQoL in MS management continues to increase. Integrating MI training into rehabilitation programs may provide significant benefits, allowing MS patients to live more active, meaningful lives.

Ethics

Conflict of Interest: The author declare no conflict of interest.

Financial Disclosure: The author declared that this study received no financial support.

References

1. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and Treatment of Multiple Sclerosis: A Review. JAMA. 2021;325:765-779.
2. The Multiple Sclerosis International Federation, Atlas of MS, 3rd Edition. 2020.
3. Murray TJ. Diagnosis and treatment of multiple sclerosis. BMJ. 2006;332:525-527.
4. Kahraman T, Temiz H, Abasiyanik Z, Baba C, Ozakbas S. Dual-task difficulties as a risk factor for unemployment in people with multiple sclerosis. Brain Behav. 2023;13:e3299.
5. Benito-León J, Morales JM, Rivera-Navarro J, Mitchell A. A review about the impact of multiple sclerosis on health-related quality of life. Disabil Rehabil. 2003;25:1291-303.
6. Rudick RA, Miller D, Clough JD, Gragg LA, Farmer RG. Quality of life in multiple sclerosis. Comparison with inflammatory bowel disease and rheumatoid arthritis. Arch Neurol. 1992;49:1237-1242.
7. Petajan JH, Gappmaier E, White AT, Spencer MK, Mino L, Hicks RW. Impact of aerobic training on fitness and quality of life in multiple sclerosis. Ann Neurol. 1996;39:432-441.
8. Mulder T. Motor imagery and action observation: cognitive tools for rehabilitation. J Neural Transm (Vienna). 2007;114:1265-1278.
9. Singer T, Fahey P, Liu KPY. Effectiveness of Motor Imagery in the Rehabilitation of People With Parkinson's Disease: A Systematic Review and Meta-Analysis. Neurorehabil Neural Repair. 2024;38:460-475.
10. Zhao LJ, Jiang LH, Zhang H, Li Y, Sun P, Liu Y, Qi R. Effects of Motor Imagery Training for Lower Limb Dysfunction in Patients With Stroke: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Am J Phys Med Rehabil. 2023;102:409-418.
11. Gil-Bermejo-Bernardez-Zerpa A, Moral-Munoz JA, Lucena-Anton D, Luque-Moreno C. Effectiveness of Motor Imagery on Motor Recovery in Patients with Multiple Sclerosis: Systematic Review. Int J Environ Res Public Health. 2021;18:498.
12. Agostini F, Pezzi L, Paoloni M, Insabella R, Attanasi C, Bernetti A, Saggini R, Mangone M, Paolucci T. Motor Imagery: A Resource in the Fatigue Rehabilitation for Return-to-Work in Multiple Sclerosis Patients-A Mini Systematic Review. Front Neurol. 2021;12:696276.
13. Seebacher B, Reindl M, Kahraman T. Factors and strategies affecting motor imagery ability in people with multiple sclerosis: a systematic review. Physiotherapy. 2023;118:64-78.
14. Ruffino C, Papaxanthis C, Lebon F. Neural plasticity during motor learning with motor imagery practice: Review and perspectives. Neuroscience. 2017;341:61-78.
15. Lubetzki C, Stankoff B. Demyelination in multiple sclerosis. Handb Clin Neurol. 2014;122:89-99.
16. Hétu S, Grégoire M, Saimpont A, Coll MP, Eugène F, Michon PE, Jackson PL. The neural network of motor imagery: an ALE meta-analysis. Neurosci Biobehav Rev. 2013;37:930-949.

17. Tacchino A, Pedullà L, Podda J, Monti Bragadin M, Battaglia MA, Bisio A, Bove M, Brichetto G. Motor imagery has a priming effect on motor execution in people with multiple sclerosis. Front Hum Neurosci. 2023;17:1179789.
18. Loporto M, McAllister C, Williams J, Hardwick R, Holmes P. Investigating central mechanisms underlying the effects of action observation and imagery through transcranial magnetic stimulation. J Mot Behav. 2011;43:361-373.
19. Munzert J, Lorey B, Zentgraf K. Cognitive motor processes: the role of motor imagery in the study of motor representations. Brain Res Rev. 2009;60:306-326.
20. Seebacher B, Kuisma R, Glynn A, Berger T. Effects and mechanisms of differently cued and non-cued motor imagery in people with multiple sclerosis: A randomised controlled trial. Mult Scler. 2019;25:1593-1604.
21. Kahraman T, Savci S, Ozdogar AT, Gedik Z, Idiman E. Physical, cognitive and psychosocial effects of telerehabilitation-based motor imagery training in people with multiple sclerosis: A randomized controlled pilot trial. J Telemed Telecare. 2020;26:251-260.
22. Seebacher B, Kuisma R, Glynn A, Berger T. The effect of rhythmic-cued motor imagery on walking, fatigue and quality of life in people with multiple sclerosis: A randomised controlled trial. Mult Scler. 2017;23:286-296.
23. Seebacher B, Helmlinger B, Pinter D, Heschl B, Ehling R, Hechenberger S, Reindl M, Khalil M, Enzinger C, Deisenhammer F, Brenneis Md C. Actual and Imagined Music-Cued Gait Training in People with Multiple Sclerosis: A Double-Blind Randomized Parallel Multicenter Trial. Neurorehabil Neural Repair. 2024;38:555-569.
24. Hanna M, Strober LB. Anxiety and depression in Multiple Sclerosis (MS): Antecedents, consequences, and differential impact on well-being and quality of life. Mult Scler Relat Disord. 2020;44:102261.
25. Pourhaji F, Peyman N, Taraghdar MM, Jamali J, Tehrani H. Explaining the burden of psychosocial factors on the worsening symptoms of MS: a qualitative study of patients' experiences. BMC Neurol. 2023;23:98.
26. Simeoni M, Auquier P, Fernandez O, Flachenecker P, Stecchi S, Constantinescu C, Idiman E, Boyko A, Beiske A, Vollmer T, Triantafyllou N, O'Connor P, Barak Y, Biermann L, Cristiano E, Atweh S, Patrick D, Robitail S, Ammoury N, Beresniak A, Pelletier J; MusiQol study group. Validation of the Multiple Sclerosis International Quality of Life questionnaire. Mult Scler. 2008;14:219-230.
27. Hobart J, Lamping D, Fitzpatrick R, Riazi A, Thompson A. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. Brain. 2001;124:962-973.
28. Regnault A, Loubert A, Brennan R, Meunier J, Naujoks C, Cano S, Adlard N. Does the Multiple Sclerosis Impact Scale-29 (MSIS-29) have the range to capture the experience of fully ambulatory multiple sclerosis patients? Learnings from the ASCLEPIOS studies. Mult Scler J Exp Transl Clin. 2023;9:20552173231201422.
29. Ware JE, Gandek B. The SF-36 Health Survey: Development and use in mental health research and the IQOLA Project. Int J Ment Health. 1994;23:49-73.
30. Nortvedt MW, Riise T, Myhr KM, Nyland HI. Performance of the SF-36, SF-12, and RAND-36 summary scales in a multiple sclerosis population. Med Care. 2000;38:1022-1028.
31. Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: Scoping review. SAGE Open Med. 2016;4:2050312116671725.
32. Brooks R. The EuroQol group after 25 years: Springer Science & Business Media, 2012.
33. Campbell JA, Ahmad H, Chen G, van der Mei I, Taylor BV, Claflin S, Henson GJ, Simpson-Yap S, Laslett LL, Hawkes K, Hurst C, Waugh H, Palmer AJ. Validation of the EQ-5D-5L and psychosocial bolt-ons in a large cohort of people living with multiple sclerosis in Australia. Qual Life Res. 2023;32:553-568.
34. Kahraman T. Health-Related Quality of Life in Multiple Sclerosis. In: Çetişli-Korkmaz N, Bilek F (Eds). Neurorehabilitation in Multiple Sclerosis. Ankara, Hipokrat Yayıncılık, 2023, pp 277-290.

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RESEARCH ARTICLE

Cognitive Function Variability and Health-related Quality of Life in Multiple Sclerosis: A Comprehensive Analysis Across Different Multiple Sclerosis Types

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Abstract

Objective: To investigate cognitive function variability and health-related quality of life in patients with diverse types of multiple sclerosis (MS).

Materials and Methods: This study involved 780 participants diagnosed with various types of MS. Data was collected using the MS quality of life 54 questionnaire, administered online during the coronavirus disease-2019 pandemic.

Results: The cognitive function scores of the various MS types were found to be significantly distinct, with the relapsing-remitting (RR) type exhibiting the greatest variability. Repeated measures analysis of variance revealed a modest improvement in cognitive function over time in RRMS patients. Age and health-related quality of life exhibited a highly significant negative correlation ($r=-0.63$, $p<0.001$). Heritability analysis suggested that approximately 45% of cognitive function variability is attributable to genetic factors. Specifically, RRMS patients exhibited higher cognitive function scores compared to patients with primary-progressive type and secondary-progressive type of MS ($p<0.01$ and $p<0.05$, respectively).

Conclusion: Cognitive function and health-related quality of life differ significantly among the different MS types. Age and genetic factors play critical roles in cognitive health. The findings underscore the need for conducting routine cognitive assessments in MS patients, especially for those with RRMS, to provide early intervention and enhance patient outcomes. Comprehensive mean square care necessitates the integration of cognitive and physical health management strategies.

Keywords: Multiple sclerosis, cognitive dysfunction, quality of life, rehabilitation, mental health

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system that primarily impacts young adults. It is distinguished by a diverse array of symptoms, including physical, cognitive, and emotional dysfunction, which substantially compromises the quality of life of the patients (1). Genetic, environmental, and lifestyle factors can substantially influence the prevalence and clinical characteristics of MS in various geographical regions (2).

The prevalence of MS is approximately 3:1 among adults aged 20 to 50. Genetic predisposition plays a significant role, as persons with a family history of MS exhibit a higher risk of developing the disease (3). The risk of developing the disease is elevated by environmental factors, such as poor vitamin D levels, viral infections (Epstein-Barr virus), and smoking (4). The clinical course of MS can vary, with the relapsing-remitting form being the most prevalent, characterized by periods of symptom exacerbation followed by partial or complete recovery (5).

Cognitive dysregulation is a common feature of MS, affecting approximately 40-70% of patients (6). This impairment can manifest in several cognitive aspects, including memory, attention, processing speed, and executive functions. Cognitive deficits in MS are linked to lesions and atrophy in specific brain regions, such as the cortical and subcortical areas (7). The severity and profile of cognitive dysfunction can vary considerably among individuals, frequently being influenced by the type and stage of the disease (8). This study aimed to investigate cognitive function variability and health-related quality of life in 780 participants diagnosed with different types of MS.

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By focusing on these cognitive domains, this research seeks to enhance the understanding of the influence of cognitive impairments on the quality of life of MS patients and to aid the development of more effective management strategies.

The prevalence and severity of cognitive dysregulation can vary significantly across different MS subtypes, including clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS) (9). The most prevalent subtype of RRMS is characterized by periods of symptom exacerbation with partial or complete recovery, which presents an opportunity to investigate cognitive fluctuations over time. It is imperative to comprehend the variation in cognitive function among these subtypes to create targeted management strategies that can enhance patient outcomes (10). The primary aim of this study was to characterize cognitive impairment and its impact on health-related quality of life across diverse MS subtypes. Previous research has demonstrated that cognitive dysfunction is not only prevalent but also a major determinant of quality of life in MS patients. Cognitive impairment often manifests early in the disease course, affecting 40-60% of MS patients and substantially influencing employability, social interactions, and quality of life. Despite advances in neuropsychological assessments and neuroimaging studies, there are still significant ambiguities regarding the underlying mechanisms, neural basis, and effectiveness of interventions for managing cognitive impairment in MS (11).

Health-related quality of life is a multidimensional concept that encompasses physical, mental, and social well-being (12). In MS, the health-related quality of life is frequently compromised due to a combination of physical disability, cognitive impairment, fatigue, depression, and other factors (13). MS is a heterogeneous disease with multiple subtypes that exhibit distinct clinical and pathological characteristics. The main types include CIS, RR type, PP type, and SP type (14). Understanding the variation in cognitive functions across the various MS subtypes is crucial for developing individualized management strategies and improving patient outcomes (15).

Materials and Methods

This study included individuals diagnosed with various types of MS, including CIS, RRMS, PPMS, and SPMS. MS subtypes were diagnosed using the revised McDonald criteria (2017), which are widely accepted for diagnosis (16).

This research was conducted from 2020 to 2021, during the coronavirus disease-2019 (COVID-19) pandemic, using an online MS Quality of Life (MSQoL) questionnaire. The MSQoL questionnaire used in this study is a validated instrument designed to evaluate various aspects of health-related quality of life in MS patients, with a particular emphasis on cognitive functioning. The questionnaire assesses critical cognitive domains, including processing speed, attention, memory, and working memory, which are frequently impaired in MS patients. This questionnaire is globally used for MS patients due to its reliability and validity (17).

The questionnaire was distributed anonymously to safeguard the participants' privacy and confidentiality. The study enrolled 780 participants globally. The participants' freedom to decline to respond to all inquiries led to a variation in the total number of questions answered and the responses provided. The questions were administered via the online tool Google Forms. The inclusion criteria for this research were patients with MS and cognitive impairments (the determination of cognitive impairments for this was based on participants self-reported difficulties in concentration, attention, and memory as indicated by their responses) who could speak fluent English. Patients diagnosed with other neurological disorders, MS patients who do not have cognitive impairments, and patients with MS who do not speak English were excluded from this study.

The study does not require formal ethical approval due to several reasons. First, the study was conducted using anonymous online surveys to ensure the privacy and confidentiality of all participants. No personal identifiers were collected that could link the responses back to individual participants. Also, participation in the study was entirely voluntary. Participants consented to the study by completing the online questionnaire. This implied consent is adequate given the nature of the research and the minimal risk involved. The research involves minimal risk to participants, as it only required them to respond to a survey regarding their cognitive functions and quality of life. There were no interventions or manipulations that could cause physical or psychological harm. The survey did not cover sensitive topics that could distress or stigmatize the participants. It focused on cognitive function and health-related quality of life, which are general topics. Given the constraints of the COVID-19 pandemic, the study design prioritized ease of participation while maintaining ethical standards. The streamlined procedures were necessary to facilitate broad participation without compromising ethical integrity. In regard to these considerations, the study adheres to ethical research standards without the need for a formal ethics committee review.

The study was conducted anonymously to protect participants privacy and confidentiality, and participation in the online questionnaire was voluntary, implying consent upon completion. Additionally, the constraints posed by the COVID-19 pandemic necessitated streamlined procedures to ensure broad and easy participation.

Statistical Analysis

Statistical analyses were performed using the R (version 4.0.3) and Phyton (version 3.8) software with appropriate libraries for

data manipulation and statistical testing. Descriptive statistics, including mean and standard deviation, were computed for cognitive function scores across different MS subtypes. Box plots were generated to illustrate the distribution of cognitive function scores among the various MS subgroups. A one-way analysis of variance (ANOVA) was conducted to investigate the differences in cognitive function scores among the MS subtypes.

To identify particular group differences, post-hoc experiments were implemented. The Pearson correlation coefficients were calculated to determine the relationship between age and health-related quality of life. Additionally, a repeated measures ANOVA test was performed to evaluate the evolution of cognitive function among participants with RRMS over time. This analysis included time as a within-subject factor. Standard genetic modeling techniques were employed to estimate cognitive function variability by incorporating data from family studies and utilizing heritability (h^2). Lastly, a chi-square test of independence was used to determine the sex distribution across the MS subtypes. The observed frequencies were compared to the calculated expected frequencies.

Cognitive functions were evaluated using the MSQoL questionnaire, which comprises a variety of subscales designed to assess different cognitive domains such as concentration, memory, and attention retention. The composite score calculated from these subscales, which ranges from 0 to 120, is the cognitive function score reported in the results section. This score is indicative of the participants' overall cognitive health. The MSQoL questionnaire is internationally acknowledged for its reliability and validity in assessing cognitive functions in MS patients, which supports the accuracy of the data presented in this study. The scoring range (0-120) was derived by aggregating the individual scores from the cognitive subscales, where higher scores indicate greater cognitive function. This method allowed the study to capture a diverse array of cognitive abilities across the various MS subtypes. The composite scores were subsequently subjected to statistical analyses, including ANOVA, to investigate the variation in cognitive function among various MS subtypes.

The study also evaluated cognitive function in RRMS patients at three distinct time points to capture the variability in cognitive function during the various disease phases. The time points were defined as follows:

- Time point 1: During an acute relapse, when the patient's neurological symptoms are most severe. This phase was chosen to assess cognitive function under maximum disease activity.

- Time point 2: Midway through the remission phase, where there is a partial decrease in symptoms but potential ongoing cognitive challenges. This phase was chosen to observe the recovery process and its impact on cognitive health.

- Time point 3: At the conclusion of the remission phase, just prior to the next anticipated relapse, where symptoms have stabilized and cognitive function may show the most improvement.

These time points were selected to provide a thorough understanding of the cognitive function fluctuations that occur during the RRMS cycle. The repeated measures ANOVA were employed to analyze the cognitive scores at these three points, offering insights into the temporal dynamics of cognitive impairment in RRMS patients.

Results

Table 1 presents the demographic characteristics of the study participants, based on sex and age. Most participants were female (85.6%). A majority of the participants were aged 20-40.

Table 2 provides descriptive statistics regarding MS subtypes among the participants. Most participants were diagnosed with RRMS, representing 68% of the sample. There were 14% of participants with PPMS, and 13% of them had SPMS. Only 5% of the MS patients in the sample received a diagnosis of CIS.

In Table 3, the correlation between sex and MS subtypes among the study participants is illustrated. Most female participants (74.2%) and male participants (56.7%) were diagnosed with RRMS. PPMS was more common among males (26.8%) compared to females (12.8%). SP type had a relatively similar distribution between the sexes, with 13.0% of females and 16.5% of males being diagnosed with this subtype.

Table 1. Demographic characteristics of the participants

Demographic variable	Frequency (n)	Percentage (%)
Sex		
Female	593	85.6
Male	100	14.4
Age		
10-20 years	74	9
20-30 years	230	30
30-40 years	270	35
40-50 years	151	19
50-60 years	43	5
60-70 years	7	1
70-80 years	1	1

Table 2. MS subtypes among the study participants

MS subtype	Frequency	Percentage
Clinically isolated syndrome	37	5%
Relapsing-remitting MS	484	68%
Primary progressive MS	102	14%
Secondary progressive MS	90	13%

MS: Multiple sclerosis

Table 4 summarizes the frequency of cognitive issues reported by the MS patients. Concentration difficulties were experienced by 15% of participants all the time, while 34% reported these difficulties some of the time. Attention retention issues followed a similar pattern, with 14% of MS patients experiencing them all the time and 32% some of the time. 19% of participants reported that memory problems were present at all times, while 30% experienced them occasionally. Additionally, 16% of participants experienced cognitive changes that were observed by their family members all the time, while 23% reported no such changes.

The responses of participants to a variety of health-related statements are presented in Table 5, which reflects their perceptions of their health status and the impact of health issues on their well-being. A significant portion of the participants (38%) disagreed with the statement "I seem to get sick more often", while 33% were unsure. Similarly, 39% of participants disagreed with the statement "I am as healthy as anyone else", indicating concerns about their health. When asked about future health expectations, 38% were unsure, and 23% expected their health to worsen. Only 8% considered their health to be excellent.

Table 3. Relationship between multiple sclerosis subtype and sex

MS subtype	Female (%)	Male (%)
Primary progressive	12.8%	26.8%
Relapsing-remitting	74.2%	56.7%
Secondary progressive	13.0%	16.5%

MS: Multiple sclerosis

In terms of health issues, 35% of participants were uncertain whether they felt discouraged by their health problems, while 31% expressed frustration with their health status. Thirty two percent of participants expressed concern regarding their health, while thirty percent experienced fatigue as a result of frequent fluctuations in their condition. The table illustrates the diverse perspectives and apprehensions that participants have regarding their health and its impact on their daily lives.

Figure 1 illustrates cognitive function scores based on the MS subtypes. The four MS subtypes are represented on the X-axis, while the cognitive function scores are represented on the Y-axis, which spans from 0 to 120. For the CIS, the box plot displays a median score of approximately 50, an interquartile range of approximately 45-55, and a few outliers. The scores are closely clustered around the median with a limited interquartile range, indicating that there is less variability. For the RRMS subtype, the box plot exhibits a wider distribution, a median score around 60, an interquartile range approximately 45-75, and several outliers. The scores exhibit a broader spread, indicating greater variability in cognitive function among the patients. For the PP type, the box plot exhibits a median score of approximately 55 and an interquartile range of approximately 45-65. The scores are moderately dispersed, with a median value comparable to CIS and some outliers. For the SPMS, the box plot demonstrated a median score of about 50, an interquartile range of approximately 40-60, and fewer outliers compared to the other types. The scores are relatively similar to the PPMS, but they exhibit less variability.

The results of the ANOVA test-based analysis of the differences in cognitive function scores across different MS subtypes are

Table 4. Cognitive function among the participants

Cognitive problems	All the time	Most of the time	Occasionally	Rarely	Not at all
Concentration difficulties	15%	23%	34%	16%	12%
Attention retention issues	14%	23%	32%	16%	15%
Memory problems	19%	22%	30%	16%	13%
Cognitive changes noted by family members	16%	19%	23%	19%	23%

Table 5. Health-related responses from the study participants

Health statements	Definitely correct	Correct	Not sure	Definitely incorrect
I seem to get sick more often	14%	15%	33%	38%
I am as healthy as anyone else	11%	20%	30%	39%
I expect my health to worsen	23%	25%	38%	13%
My health is excellent	8%	21%	28%	43%
Health issues	**Definitely yes**	**Yes**	**Not sure**	**Definitely no**
Do you feel discouraged by your health problems?	16%	20%	35%	19%
Are you frustrated by your health?	23%	23%	31%	15%
Do you often worry about your health?	21%	24%	32%	18%
Are you often tired due to frequent changes in your condition?	30%	24%	24%	16%

presented in Table 6. The analysis reveals a significant difference between the groups, as indicated by an F-statistic of 89.24 and a p-value of less than 0.001. The intergroup sum of squares (SS) is 39,444.71, with a MS of 13,148.24 across three degrees of freedom (df). The intragroup SS is 103,056.78, with a mean square of 145.34 distributed across 709 df. These results indicate that the variability in cognitive function scores is significantly impacted by the MS subtype, justifying further analysis to explore these differences in greater detail.

The results of the repeated ANOVA test for cognitive function over time for RRMS patients are presented in Figure 2 and Table 7. This figure illustrates the alterations in cognitive function scores for RRMS patients over three distinct time points. The cognitive function scores are represented by the Y-axis, which ranges from 56 to 64. The X-axis is labeled with three time points, and the orange line connects the cognitive function scores at each time point, demonstrating a slight upward trend over time. The shaded area around the line indicates the range of variation or confidence interval (CI) for the scores. This illustrates a modest increase in the cognitive function scores of RRMS patients between time 1 and time 3. This implies that there is some variability in the scores; however, the overall trend indicates a slight improvement in cognitive function over the three time points that were observed. The repeated measures ANOVA shows a significant alteration in cognitive function scores over time among RRMS patients, with a p-value of 0.027.

The correlation analysis for age and health-related quality of life is presented in Table 8. The analysis indicates a significant negative correlation (r=-0.63; p-value <0.001). This suggests that as age increases, health-related quality of life tends to diminish among MS patients, indicating that older individuals with MS may experience more significant challenges to their quality of life.

Table 9 illustrates the h^2 analysis of cognitive function variability. The analysis revealed a h^2 estimate of 0.45, indicating that approximately 45% of the variability in cognitive function may be attributed to genetic factors. This implies a moderate genetic influence on cognitive performance among the study participants.

The chi-square test results are presented in Table 10. The observed and expected frequencies for both female and male participants are shown for each MS subtype (the PP, RR, and SP subtypes). The chi-square statistic (χ^2) is 15.10 with two df, and a p-value of 0.0005, indicating a significant difference in gender distribution among the different MS subtypes. This suggests that the distribution of MS subtypes varies significantly by sex.

The results of the post-hoc Tukey's honestly significant difference test, which was administered following the ANOVA test, are presented in Table 11. The purpose of this test was to identify specific differences in cognitive function scores between MS subtypes. The comparisons encompass RRMS vs. PPMS vs. SPMS, and PPMS vs. SPMS. The table shows the mean difference in cognitive function scores between each pair of subtypes, along with the corresponding 95% CI and p-values. Significant differences were noted between the RR type and both PP type and SPMS subtypes, indicating higher cognitive function scores in the RR group. The cognitive function profiles of the PP and SP forms of MS were found to be more similar, as no significant difference was observed.

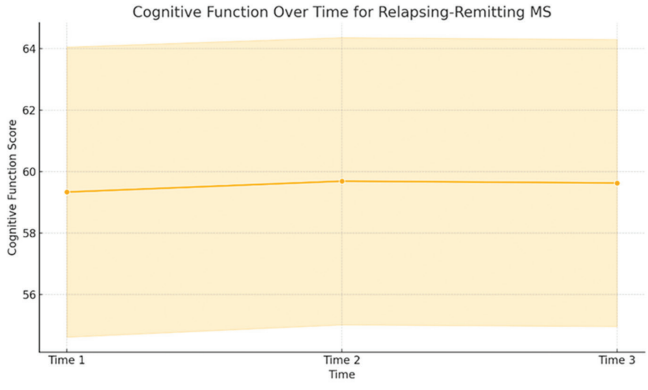

Figure 2. Repeated ANOVA test - cognitive function over time for relapsing remitting type of MS

MS: Multiple sclerosis

Discussion

This study investigated the cognitive characteristics and health-related problems in MS patients.

It is essential to recognize that depression and fatigue are common symptoms in MS patients and can significantly

Table 7. Repeated measures ANOVA test

Source of variation	Degrees of freedom	F-statistic	p-value
Time	2	3.64	0.027
Residual	966		

Table 6. ANOVA test analysis of cognitive function scores

Source of variation	Sum of squares	Degrees of freedom	Mean square	F-statistic	p-value
Inter-group	39444.71	3	13148.24	89.24	<0.001
Intra-group	103056.78	709	145.34		
Total	142501.49	712			

influence quality of life. Both depression and fatigue are known to influence cognitive function, potentially exacerbating cognitive dysfunction and diminishing general quality of life. Although our research focused on cognitive function variability among patients with various MS subtypes, the lack of direct assessment of depression and fatigue represents a limitation. Notably, there are research papers that highlight this issue, as evidenced by the fact that 62% of MS patients experienced mild depression (13).

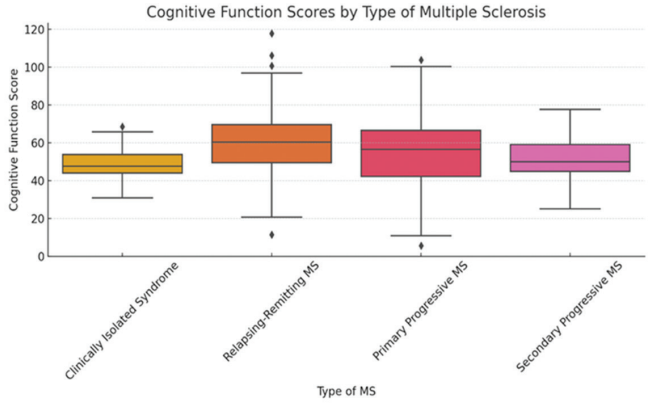

Figure 1. Cognitive function scores by multiple sclerosis subtypes
MS: Multiple sclerosis

Our findings are consistent with previous research that emphasizes the significance of cognitive impairment in RRMS. Wu et al.'s (18) study emphasizes the necessity of routine cognitive screening in the management of RRMS. This study demonstrates that the early identification of cognitive impairments can result in timely interventions, improved patient outcomes, and more effective treatment strategies. Considering that a significant proportion of RRMS patients exhibited cognitive impairment in our study, we firmly advocate for the incorporation of routine cognitive assessments into the standard care protocol for RRMS patients. This approach could substantially enhance the quality of life for RRMS patients and facilitate more effective management of cognitive symptoms (18).

The current study's results align with those of a cross-sectional study by Nabizadeh et al. (19) that investigated the relationship between cognitive impairment and quality of life in RRMS patients. This study emphasizes the necessity of an integrated approach to MS management that encompasses both cognitive and physical aspects of the disease. Enhanced cognitive function may not only strengthen individual cognitive abilities but also contribute to a higher quality of life. Similarly, our findings indicate that including routine cognitive assessments and targeted interventions in the care of RRMS patients could promote comprehensive patient well-being and optimize treatment outcomes (19).

Table 8. Correlation analysis between age and health-related quality of life

Variable 1	Variable 2	Correlation coefficient (r)	p-value
Age	Health-related quality of life	-0.63	<0.001

Table 9. Heritability analysis for cognitive function variability

Trait	Heritability estimate	Interpretation
Cognitive function	0.45	Moderate genetic influence

Table 10. Chi-square test results

MS subtype	Female (observed)	Female (expected)	Male (observed)	Male (expected)
Primary progressive	72	83.55	26	14.45
Relapsing-remitting	416	401.57	55	69.43
Secondary progressive	73	75.88	16	13.12
Statistics			**Value**	
Statistic (χ^2)			15.10	
Degrees of freedom			2	
p-value			0.0005	
Conclusion			**Significant**	

MS: Multiple sclerosis

Table 11. Post-hoc comparisons of cognitive function scores between the various multiple sclerosis subtypes

Comparison	Mean difference	95% CI	p-value
Relapsing-remitting vs. primary-progressive	5.00	(3.00, 7.00)	<0.01
Relapsing-remitting vs. secondary-progressive	4.50	(2.50, 6.50)	<0.05
Primary-progressive vs. secondary-progressive	0.50	(-1.00, 2.00)	>0.05

CI: Confidence intervals

A comprehensive review by Gómez-Melero et al. (20) focused on the major impact of cognitive impairment on quality of life of MS patients. This review underscores the complex interaction between cognitive dysfunction and various aspects of quality of life, noting that these effects can be profound even in the early stages of the disease. Similarly, our study illustrates that cognitive impairments in MS patients are strongly linked to a diminished quality of life. This underscores the need for early and comprehensive cognitive assessments in the management of the disease (20).

Schreiner et al. (21) conducted an additional exhaustive analysis that investigates the risk factors associated with cognitive impairment in MS and its effect on quality of life. This analysis offers insight into the profound impact cognitive deficits can have on mental functions, including learning, memory, perception, and problem solving abilities that are essential for daily functioning and overall health. Our research shows that cognitive impairments in patients with MS are not only prevalent but also significantly burden their quality of life. These results highlight the urgent need for early identification and targeted interventions to mitigate the effects of cognitive deficits and promote improved general outcomes for MS patients (21).

Our study's results corroborate the findings of David et al. (22), a study that examined the cognitive, clinical, and imaging characteristics of patients with benign MS at a specialized MS Center in Campinas, Brazil. The study revealed that nearly 60% of participants were affected by deficits in at least one cognitive domain, with visual memory being the most frequently affected, despite the extended disease duration and low expanded disability status scale scores in these patients. Our research suggests that cognitive impairments are prevalent even in patients with benign MS forms. These findings suggest that cognitive impairments are a significant concern across all MS subtypes and reinforce the need for routine cognitive assessments, regardless of the perceived disease severity (22).

Our study's conclusions are consistent with the work of Elshehawy et al. (23), which provides valuable insights into the cognitive impairment observed in adult MS patients during the remission phase. This study supports the idea that cognitive impairments should be a critical element of MS management strategies, as it demonstrates that cognitive deficits can persist even when other symptoms are less active. Our research highlights the need for routine cognitive assessments, as it recognizes that cognitive impairments can lead to more effective treatment plans and a significant improvement in the patients' quality of life. Incorporating cognitive evaluations into regular care for MS patients even during remission is crucial for optimizing long-term outcomes (23).

Faraclas et al. (24) concentrated on the substantial influence of RRMS on health-related quality of life, particularly in terms of social function, physical function, and mental health. This research demonstrates that RRMS patients report lower scores across all quality of life subscales than the general population, with a decline in mental health, especially among those who have been recently diagnosed. Consistent with our findings, nearly half of the participants in this study were at risk for depression, underscoring the critical need to prioritize mental health concerns in MS care. Our research further supports the notion that, despite the importance of physical health challenges, mental health issues should be given equal, if not greater attention, particularly early in the disease course. The general well-being and quality of life of RRMS patients could be substantially enhanced by incorporating mental health support into routine MS care (24).

In our study, we ensured that participants had the option to skip any questions they were uncomfortable answering, which may have contributed to some variability in response rates across different sections of the questionnaire. Specifically, the proportion of unanswered questions varied slightly depending on the section, but overall, the response rate was high. According to our data, the overall proportion of unanswered queries was low. For instance, the demographic section had a near-complete response rate, with only 1.4% of participants failing to respond to certain questions. This was consistent across other sections of the questionnaire, where the vast majority of questions were answered by nearly all participants. The study's findings are unlikely to be substantially influenced by the missing data, as evidenced by the minimal proportion of unanswered questions. We have included appropriate statistical methods to address any missing data, ensuring that the results presented are reliable.

Study Limitations

This study has several limitations, including sample bias. While the COVID-19 pandemic was underway, the demographics and responses of the participants may have been affected by the online format of the study. This could potentially exclude a portion of the MS population, as only those with internet access and the capacity to use online tools could participate. Additionally, the reliance on self-report questionnaires may have introduced bias. The participant's perceptions of their cognitive function and quality of life may not accurately reflect their actual condition. The study included only participants who spoke English fluently, which may limit the generalizability of the findings to non-English-speaking MS patients. The exclusion of patients with other neurological disorders and those without cognitive impairments resulted in a sample that did not fully represent the diversity of the MS population. The study's cross-sectional design does not permit the evaluation of alterations in cognitive function and quality of life over time. Longitudinal studies would be necessary to understand the progression of these variables in MS patients.

Future research should integrate a comprehensive evaluation of depression, fatigue, and cognitive function to achieve a more holistic understanding of the factors influencing quality of life in MS patients. Integrating these assessments could offer valuable information regarding the physical, emotional, and cognitive health of MS patients, thereby facilitating the development of more effective and individualized interventions.

Conclusion

This study provides a thorough analysis of cognitive function variability and health-related quality of life across different MS subtypes. The study's findings indicate significant disparities in cognitive function scores among the diverse MS subtypes, focusing on the impact of the disease on cognitive health. The ANOVA test results indicate a substantial variation in cognitive function across the MS subtypes, with RRMS exhibiting the greatest variability.

As evidenced by the repeated measures ANOVA, individuals with RRMS exhibited a modest improvement in cognitive function over time. This implies that while cognitive function can fluctuate, there is potential for improvement with appropriate interventions. The negative correlation between age and health-related quality of life is underscored by the correlation analysis, which highlights the escalating obstacles that older people with MS encounter. Additionally, the h^2 analysis demonstrates a moderate genetic influence on cognitive function variability, suggesting that both genetic and environmental factors play crucial roles in cognitive health among MS patients.

The chi-square test results reveal significant gender differences in the distribution of MS subtypes, which could have implications for customized treatment approaches. The research emphasized the importance of incorporating cognitive assessments in routine care for MS patients, particularly for those with RR types, to promote early intervention and improve general quality of life. In summary, the significance of cognitive impairments and health-related quality of life in individuals with MS is underscored by this study.

Ethics

Ethics Committee Approval: The study does not require formal ethical approval.

Informed Consent: The study was conducted anonymously to protect participants privacy and confidentiality, and participation in the online questionnaire was voluntary.

Authorship Contributions

Concept: D.A., Data Collection or Processing: D.A., Analysis or Interpretation: D.A., A.J., Literature Search: D.A., D.P., Writing: D.A., A.J.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Ghasemi N, Razavi S, Nikzad E. Multiple Sclerosis: Pathogenesis, Symptoms, Diagnoses and Cell-Based Therapy. Cell J. 2017;19:1-10.
2. Waubant E, Lucas R, Mowry E, Graves J, Olsson T, Alfredsson L, Langer-Gould A. Environmental and genetic risk factors for MS: an integrated review. Ann Clin Transl Neurol. 2019;6:1905-1922.
3. Patsopoulos NA. Genetics of Multiple Sclerosis: An Overview and New Directions. Cold Spring Harb Perspect Med. 2018;8:a028951.
4. Løken-Amsrud KI, Lossius A, Torkildsen Ø, Holmøy T. Impact of the environment on multiple sclerosis. Tidsskr Nor Laegeforen. 2015;135:856-860.
5. Klineova S, Lublin FD. Clinical Course of Multiple Sclerosis. Cold Spring Harb Perspect Med. 2018;8:a028928.
6. Morrow SA, Baldwin C, Alkabie S. Importance of Identifying Cognitive Impairment in Multiple Sclerosis. Can J Neurol Sci. 2023;50:813-819.
7. Gaetani L, Salvadori N, Chipi E, Gentili L, Borrelli A, Parnetti L, Di Filippo M. Cognitive impairment in multiple sclerosis: lessons from cerebrospinal fluid biomarkers. Neural Regen Res. 2021;16:36-42.
8. Benedict RHB, Amato MP, DeLuca J, Geurts JJG. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. Lancet Neurol. 2020;19:860-871.
9. Brochet B, Clavelou P, Defer G, De Seze J, Louapre C, Magnin E, Ruet A, Thomas-Anterion C, Vermersch P. Cognitive Impairment in Secondary Progressive Multiple Sclerosis: Effect of Disease Duration, Age, and Progressive Phenotype. Brain Sci. 2022;12:183.
10. Prajjwal P, Marsool MDM, Asharaf S, Inban P, Gadam S, Yadav R, Vora N, Nandwana V, Marsool ADM, Amir O. Comparison of recent updates in genetics, immunology, biomarkers, and neuroimaging of primary-progressive and relapsing-remitting multiple sclerosis and the role of ocrelizumab in the management of their refractory cases. Health Sci Rep. 2023;6:e1422.
11. Macías Islas MÁ, Ciampi E. Assessment and Impact of Cognitive Impairment in Multiple Sclerosis: An Overview. Biomedicines. 2019;7:22.
12. Yin S, Njai R, Barker L, Siegel PZ, Liao Y. Summarizing health-related quality of life (HRQOL): development and testing of a one-factor model. Popul Health Metr. 2016;14:22.
13. Sehanovic A, Kunic S, Ibrahimagic OC, Smajlovic D, Tupkovic E, Mehicevic A, Zoletic E. Contributing Factors to the Quality of Life in Multiple Sclerosis. Med Arch. 2020;74:368-373.
14. National Multiple Sclerosis Society. Types of MS. National Multiple Sclerosis Society. Retrieved from https://www.nationalmssociety.org/understanding-ms/what-is-ms/types-of-ms.
15. van Dam M, Krijnen EA, Nauta IM, Fuchs TA, de Jong BA, Klein M, van der Hiele K, Schoonheim MM, Hulst HE. Identifying and understanding cognitive profiles in multiple sclerosis: a role for visuospatial memory functioning. J Neurol. 2024;271:2195-2206.
16. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara K, Galetta SL, Hartung HP, Kappos L, Lublin FD, Marrie RA, Miller AE, Miller DH, Montalban X, Mowry EM, Sorensen PS, Tintoré M, Traboulsee AL, Trojano M, Uitdehaag BMJ, Vukusic S, Waubant E, Weinshenker BG, Reingold SC, Cohen JA. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17:162-173.
17. Soares R, Kops PN, Vicenzi J, Finkelzstejn A, Picon PD. Reliability, Sensitivity and Validity of the MSQoL-54 Instrument: Brazilian Version. Arch Neurol Neurol Disord. 2021;4:127.
18. Wu W, Francis H, Lucien A, Wheeler TA, Gandy M. The Prevalence of Cognitive Impairment in Relapsing-Remitting Multiple Sclerosis: A Systematic Review and Meta-analysis. Neuropsychol Rev. 2024.

19. Nabizadeh F, Balabandian M, Rostami MR, Owji M, Sahraian MA, Bidadian M, Ghadiri F, Rezaeimanesh N, Moghadasi AN. Association of cognitive impairment and quality of life in patients with multiple sclerosis: A cross-sectional study. Curr J Neurol. 2022;21:144-150.
20. Gómez-Melero S, Caballero-Villarraso J, Escribano BM, Galvao-Carmona A, Túnez I, Agüera-Morales E. Impact of Cognitive Impairment on Quality of Life in Multiple Sclerosis Patients-A Comprehensive Review. J Clin Med. 2024;13:3321.
21. Schreiner TG, Mihoc I, Grigore E, Schreiner OD. Risk Factors for Cognitive Impairment in Multiple Sclerosis Patients. Sclerosis. 2024;2:77-87.
22. David JA, De Paula TV. Cognitive, clinical and image analysis of multiple sclerosis patients. In: Proceedings of the BCTRIMS 24th Annual Meeting, 2023, São Paulo. Anais eletrônicos. Campinas: Galoá, 2023. Available from: https://proceedings.science/bctrims-2023/papers/cognitive-clinical-and-image-analysis-of-multiple-sclerosis-patients?lang=en.
23. Elshehawy SE, Ibrahim IMA, Abdel-Naby AM, Khater MEH. Cognitive impairment in a sample of adult patients with multiple sclerosis: an Egyptian study. Middle East Curr Psychiatry. 2023;30:80.
24. Faraclas E, Lynn J, Lau JD, Merlo A. Health-Related Quality of Life in people with Multiple Sclerosis: How does this Population Compare to Population-based Norms in Different Health Domains? J Patient Rep Outcomes. 2022;6:12.

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RESEARCH ARTICLE

Natalizumab in Multiple Sclerosis: A Single Centre Real-World Study

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Abstract

Objective: Natalizumab (NTZ) is an effective immunomodulator therapy (IMT) employed for multiple sclerosis (MS) therapy. This study aimed to investigate the efficacy and safety of NTZ treatment in MS patients.

Materials and Methods: Patients with clinically definite MS who received NTZ treatment were included in the study, and their data were derived from the iMed database. Patient demographics such as age, sex, and disease duration were assessed. The results pertaining to the annual number of attacks, expanded disability status scale (EDSS) results, magnetic resonance data, and no evidence of disease activity-3 (NEDA-3) were obtained.

Results: This study included 153 patients (108 female and 43 male). The patients' ages ranged from 21.63 to 67.60 years, with a mean age of 44.50 years. Prior to undergoing NTZ treatment, 54.3% of the patients had received at least two other IMTs. The mean annual number of assaults was 1.19, and the number of attacks in the year prior to treatment ranged from 0 to 6. The mean number of attacks in the first year following treatment was 0.07, 0.13 in the second year, and 0.09 in the third year. The baseline EDSS values of the patients varied between 0 and 5.5, and the mean baseline EDSS value was 3.08. During the initial year of treatment, the patient's mean EDSS value was 2.58, the second year was 2.32, and the third year was 2.34. Recurrence with increased severity of disease activity or rebound development was observed in 14.6% of the patients whose NTZ treatment was terminated for any reason. The NEDA-3 value decreased from 82.8% (n=145) in the first year to 77.3% (n=132) in the second year and 79.0% (n=81) in the third year.

Conclusion: Patients received NTZ for three years on average. 14.6% of the patients exhibit a recurrence or rebound of disease activity. Anti-John Cunningham virus antibody was detected in 5% of patients during the course of treatment. Approximately 80% of patient achieved NEDA-3 while receiving NTZ over the three-year period.

Keywords: Multiple sclerosis, immunomodulatory therapy, natalizumab, real-world data

Introduction

Natalizumab (NTZ) is a highly efficacious treatment alternative for multiple sclerosis (MS). A 68% decrease in the annualized number of attacks (ARR) is observed with NTZ treatment compared to the placebo (1). NTZ is a high-efficiency immunomodulatory therapy (IMT). It may be a viable option, particularly for patients whose disease activity cannot be managed with first-line therapies. In recent years, NTZ has been characterized by its safety during pregnancy, in addition to its high efficacy. However, despite its effectiveness, NTZ cannot be administered for extended periods due to the risk of developing progressive multifocal leukoencephalopathy (PML), which is caused by the John Cunningham virus (JCV) (2,3). Efficacy and safety data for IMTs utilized in MS patients are first acquired from clinical trials. The outcomes of extended data from clinical trials and real-world results are also present. Furthermore, clinicians may be drawn to real-world data. Real-world data is of the utmost importance to clinicians. Real-world studies may be more intriguing than clinical trials, which are conducted with a limited number of patients. Clinicians may observe implementations that are similar or different from their own. In this respect, experiences spanning many years may be even more significant. The use of NTZ for an extended period may be impeded by the use of immunosuppression prior to IMT, the presence of anti-JCV antibodies, and prolonged use of IMTs (3,4). NTZ may have fewer real-world data than other MS IMTs, and patient data may be scarce for long-term drug use.

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This study aimed to present the efficacy and safety data of NTZ treatment for MS patients at a single center.

Materials and Methods

Patients who were diagnosed with clinically definite MS based on the McDonald 2017 criteria and were administered NTZ for at least six months were included in the study. The study included patients who were currently under treatment, as well as those who had previously received NTZ and had their treatment terminated for any reason. The study excluded patients with incomplete clinical and demographic data, those with insufficient follow-up periods, and those with comorbidities other than MS that would alter clinical findings. The patient data were accessed from the iMed database. The entries to the iMed database were made in real time for patients who were receiving NTZ treatment. Retrospective data entry could not be made in the database. We included results of radiological evaluations that were conducted by MS specialists with extensive experience in the field, in addition to demographic data pertaining to age, sex, disease duration, and the number of attacks. Expanded disability status scale (EDSS) scoring was performed by neurostatus certified specialists. Magnetic resonance imaging (MRI) findings, EDSS values, and the ARR were used to evaluate the no evidence of disease activity-3 (NEDA-3) results.

Statistical Analysis

Demographic data, including age, sex, and disease duration, are presented as the minimum, maximum, and mean ± standard deviation. The annual number of attacks, MRI findings, and EDSS values are expressed as percentages (%).

Results

This study included 151 patients (108 females and 43 males). The female/male value was 2.51. The patients' ages ranged from 21.63 to 67.60 years, with a mean age of 44.50±10.01. A family history of MS was present in 17 patients (11.3%), with the prevalent family history being the occurrence of MS in a sibling. Although all patients were experiencing relapsing remitting MS when NTZ treatment was initiated, 14 patients transitioned to the secondary progressive form of MS at the end of the study. NTZ treatment was discontinued in all these patients. During NTZ treatment, disease progression occurred only in six patients, while the remaining patients underwent this transformation in the post-NTZ period. Demographic data are illustrated in Table 1. Four patients (2.6%) received NTZ as their initial treatment, while all other patients received NTZ after at least one IMT. In terms of previous treatments, interferon use was the most common. Sixty-five patients (43%) received NTZ as the second line IMT, while 54.3% were administered at least two IMTs before NTZ treatment. Although the disease duration ranged between 2.73 and 30.66 years, the mean disease duration was 16.08±6.59 years. Disease duration at the time of initiation of NTZ treatment ranged between 0.27 and 26.68 years, with a mean of 9.93±6.26 years. The most common reasons for transitioning to NTZ treatment were frequent attacks and EDSS progression (30-42%). The number of attacks in the last year before treatment varied between 0 and 6; however, the mean annual number of attacks was 1.19. In the first year following treatment, the mean number of attacks was 0.07, followed by 0.13 in the second year and 0.09 in the third year. The baseline EDSS values of the patients ranged between 0 and 5.5, and the mean baseline EDSS value was 3.08±1.79. The mean EDSS value during the first year of treatment was 2.58, followed by 2.32 in the second year and 2.34 in the third year (Figure 1).

NTZ treatment is still being administered to 53 study patients. Among patients who discontinued NTZ treatment, the average duration of drug use was 2.71 years (2.34) years, with a range of 0.5 to 11.2 years. The duration of drug use in patients who were still on treatment ranged from 0.5 to 10.99 years, with a mean of 3.53±2.45 years. The duration of drug use for all patients was 0.5-11.2 years with a mean of 3.11±2.42 years. The most prevalent reason for NTZ termination was an increase in EDSS (30.7%). The other reasons included planned discontinuation (expiry of drug use), JCV positivity, pregnancy planning, side effects, and

Table 1. Demographic data

	Minimum	Maximum	Mean ± SD
Age	21.63	67.60	44.50±10.01
Disease duration (year)	0.27	26.68	9.93±6.26
Duration of use of natalizumab (year)	0.50	11.20	3.11±2.42
Annual number of attacks before treatment	0.00	6.00	1.19±2.12
Basal EDSS	0.00	5.50	3.08±1.79

SD: Standard deviation, EDSS: Expanded disability status scale

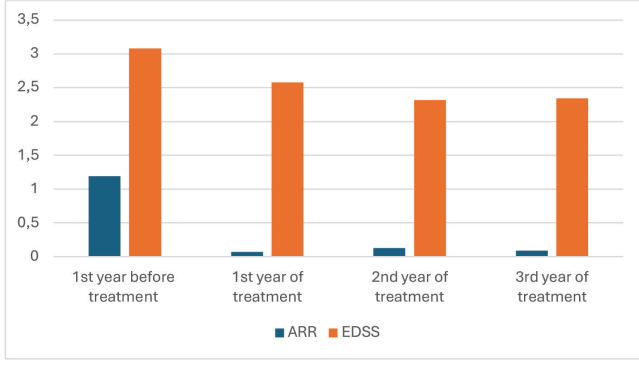

Figure 1. Impact data

ARR: Annual number of attacks, EDSS: Expanded disability status scale

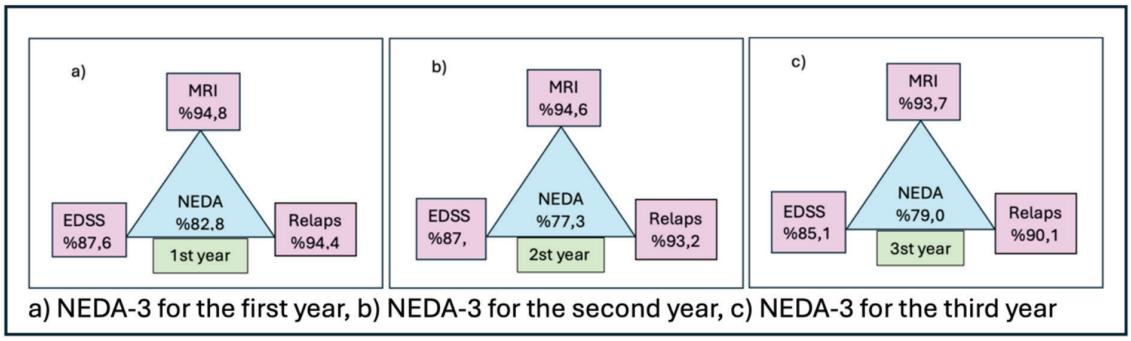

Figure 2. NEDA Outcomes

NEDA: No evidence of disease activity, EDSS: Expanded disability status scale, MRI: Magnetic resonance imaging

patient preference to discontinue NTZ. Frequent flare-ups and increased MRI activity led to the discontinuation of treatment in 8% of patients. Return of high disease activity or rebound activity was observed in 14.6% of patients whose treatment was terminated for any reason. Only three patients experienced severe adverse effects in the form of infusion reactions. These side effects occurred in doses 1, 3, and 7. In 5% of the patients with negative JCV values at the time of NTZ initiation, a return to positive serology was observed during the follow-up period. The NEDA-3 data evaluating ARR status, MRI activity, and EDSS progression were calculated for each year in the three-year period. The NEDA-3 value was 82.8% (n=145) in the first year, 77.3% (n=132) in the second year, and 79.0% (n=81) in the third year (Figure 2).

Discussion

In recent years, the utilization of highly effective IMTs has become increasingly prevalent in the clinical setting of MS. For nearly two decades, NTZ has been utilized in MS treatment and remains one of the most effective treatment options. The prominence of highly effective treatment options in MS practice has been further bolstered by the increase in their availability and prevalence over the past decade. Horizontal transitions between platform treatments in stepwise treatment applications have decreased recently. When disease activity cannot be controlled, switching to the next step in the treatment has become more rapid (6). Although it is possible to use highly effective treatments at the outset, this approach is prohibited by the health authorities in several countries. Therefore, NTZ could be employed as first-line treatment for a very limited number of patients in our study. Our data reveal that NTZ was typically used as a second and mostly as a third choice. Another reason for this situation is that our study included data from approximately 15 years prior. This is also the reason why the average duration of the disease during the NTZ initiation period was nearly ten years.

The mean ARR of the patients during the period when NTZ was initiated was as high as 1.19 in our study. The fact that this number decreased to 0.1s within a three-year period may suggest highly effective disease activity control. This effect on ARR is higher than the clinical study data for NTZ and more consistent with real-world data (1,2,4,7,8). It is observed that the mean EDSS value, which was 3.08 at the commencement of treatment, decreased to 2.5 or even lower over the course of the three-year treatment period.

The most frequent reason for the restricting the use of NTZ is JCV serological positivity. Compared to the periods when the treatment was first employed, JCV-related treatment management is more readily understood today. The risk of PML can be determined based on anti-JCV positivity, past immunosuppressive use and duration of drug use (9,10). In our study, seroconversion developed and positive anti-JCV test occurred in 5% of patients during the course of drug use (mean 3.11 years). Treatment planning for these patients was appropriately modified to include an alternative treatment mode. The annual conversion for seronegative patients has not been determined in any study published in the literature. It is not possible to access this information due to regional differences. This study has revealed that JCV seroconversion occurs at an annual rate of less than 2%, even if the number of patients is limited.

Return of high disease activity or rebound may be observed in patients receiving NTZs when treatment is discontinued for any reason. These two conditions may be confused with each other. In our series, return of elevated disease activity or rebound was observed in 14.6% of patients. Although the literature contains wide ranges for this percentage in the literature (11-16), the sum of incidence of both the conditions in our series was lower than the general data in the literature. The primary reason for this may be that we established appropriate plans for the implementation of an effective alternative treatment following NTZ.

In recent years, the most frequently employed definition for the efficacy data of IMTs used in MS treatment is NEDA. As the number of parameters evaluated increases, the NEDA score also increases. NEDA-3 is the most commonly used endpoint for evaluating efficacy of MS treatment in clinical practice. Patients with no relapse, no increase in EDSS score, and no new-active-growing lesion on MRI are patients who meet the NEDA-3 criteria. (17,18). We obtained the NEDA-3 value, in which relapse, EDSS, and MRI findings were evaluated together at rates up to 80% over a three-year period. This rate is higher than that mentioned in clinical studies published in literature. It is either high or comparable to real-world studies (19-22).

Study Limitations

Our study presents data from a single center. Therefore, it may not adequately reflect heterogeneous and universal information. Furthermore, our study, which was designed as a retrospective data screening, is less comprehensive than prospectively conducted studies. A significant limitation of this study was that cognitive functions were not assessed.

Conclusion

NTZ therapy has been used to treat MS patients because of its efficacy and safety. Patients received NTZ treatment for three years on average. In 14.6% of patients, return of disease activity or rebound was noted after the treatment was discontinued. Anti-JCV antibody was detected in 5% of patients during the course of the treatment. Approximately 80% of patients fulfilled NEDA-3 criteria during NTZ treatment over a three-year period. It is imperative to conduct comprehensive and multicenter studies that analyze real-world data from patients who are receiving natalizumab treatment. Future prospective studies are required to obtain more detailed results regarding the safety of treatment.

Ethics

Ethics Committee Approval: Ethics Committee approval is not required.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.Ö., S.Ş., M.T., Concept: A.Ö., S.Ş., Design: S.Ş., Data Collection or Processing: A.Ö., S.Ş., M.T., Analysis or Interpretation: S.Ş., Literature Search: A.Ö., S.Ş., Writing: A.Ö., S.Ş., M.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, Phillips JT, Lublin FD, Giovannoni G, Wajgt A, Toal M, Lynn F, Panzara MA, Sandrock AW; AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354:899-910.
2. Havrdova E, Galetta S, Hutchinson M, Stefoski D, Bates D, Polman CH, O'Connor PW, Giovannoni G, Phillips JT, Lublin FD, Pace A, Kim R, Hyde R. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study. Lancet Neurol. 2009;8:254-260.
3. Butzkueven H, Kappos L, Pellegrini F, Trojano M, Wiendl H, Patel RN, Zhang A, Hotermans C, Belachew S; TYSABRI Observational Program (TOP) Investigators. Efficacy and safety of natalizumab in multiple sclerosis: interim observational programme results. J Neurol Neurosurg Psychiatry. 2014;85:1190-1197.
4. Butzkueven H, Kappos L, Wiendl H, Trojano M, Spelman T, Chang I, Kasliwal R, Jaitly S, Campbell N, Ho PR, Licata S; Tysabri Observational Program (TOP) Investigators. Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri Observational Program (TOP). J Neurol Neurosurg Psychiatry. 2020;91:660-668.
5. Yamout B, Al-Jumah M, Sahraian MA, Almalik Y, Khaburi JA, Shalaby N, Aljarallah S, Bohlega S, Dahdaleh M, Almahdawi A, Khoury SJ, Koussa S, Slassi E, Daoudi S, Aref H, Mrabet S, Zeineddine M, Zakaria M, Inshasi J, Gouider R, Alroughani R. Consensus recommendations for diagnosis and treatment of Multiple Sclerosis: 2023 revision of the MENACTRIMS guidelines. Mult Scler Relat Disord. 2024;83:105435.
6. Clerico M, Artusi CA, Liberto AD, Rolla S, Bardina V, Barbero P, Mercanti SF, Durelli L. Natalizumab in Multiple Sclerosis: Long-Term Management. Int J Mol Sci. 2017;18:940.
7. Guger M, Enzinger C, Leutmezer F, Di Pauli F, Kraus J, Kalcher S, Kvas E, Berger T; Austrian MS Treatment Registry (AMSTR). Long-term outcome and predictors of long-term disease activity in natalizumab-treated patients with multiple sclerosis: real life data from the Austrian MS Treatment Registry. J Neurol. 2021;268:4303-4310.
8. Pucci E, Giuliani G, Solari A, Simi S, Minozzi S, Di Pietrantonj C, Galea I. Natalizumab for relapsing remitting multiple sclerosis. Cochrane Database Syst Rev. 2011:CD007621.
9. Plavina T, Subramanyam M, Bloomgren G, Richman S, Pace A, Lee S, Schlain B, Campagnolo D, Belachew S, Ticho B. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. Ann Neurol. 2014;76:802-812.
10. Lanza Cariccio V, Bramanti P, Mazzon E. Biomarkers identification for PML monitoring, during Natalizumab (Tysabri®) treatment in Relapsing-Remitting Multiple Sclerosis. Mult Scler Relat Disord. 2018;20:93-99.
11. Prosperini L, Kinkel RP, Miravalle AA, Iaffaldano P, Fantaccini S. Post-natalizumab disease reactivation in multiple sclerosis: systematic review and meta-analysis. Ther Adv Neurol Disord. 2019;12:175628641983780.
12. Iaffaldano P, Lucisano G, Pozzilli C, Brescia Morra V, Ghezzi A, Millefiorini E, Patti F, Lugaresi A, Zimatore GB, Marrosu MG, Amato MP, Bertolotto A, Bergamaschi R, Granella F, Coniglio G, Tedeschi G, Sola P, Lus G, Ferrò MT, Iuliano G, Corea F, Protti A, Cavalla P, Guareschi A, Rodegher M, Paolicelli D, Tortorella C, Lepore V, Prosperini L, Saccà F, Baroncini D, Comi G, Trojano M; Italian iMed-Web database. Fingolimod versus interferon beta/glatiramer acetate after natalizumab suspension in multiple sclerosis. Brain. 2015;138:3275-3586.
13. Prosperini L, Annovazzi P, Capobianco M, Capra R, Buttari F, Gasperini C, Galgani S, Solaro C, Centonze D, Bertolotto A, Pozzilli C, Ghezzi A.

Natalizumab discontinuation in patients with multiple sclerosis: Profiling risk and benefits at therapeutic crossroads. Mult Scler. 2015;21:1713-1722.

14. Clerico M, Schiavetti I, De Mercanti SF, Piazza F, Gned D, Brescia Morra V, Lanzillo R, Ghezzi A, Bianchi A, Salemi G, Realmuto S, Sola P, Vitetta F, Cavalla P, Paolicelli D, Trojano M, Sormani MP, Durelli L. Treatment of relapsing-remitting multiple sclerosis after 24 doses of natalizumab: evidence from an Italian spontaneous, prospective, and observational study (the TY-STOP Study). JAMA Neurol. 2014;71:954-960.
15. Sorensen PS, Koch-Henriksen N, Petersen T, Ravnborg M, Oturai A, Sellebjerg F. Recurrence or rebound of clinical relapses after discontinuation of natalizumab therapy in highly active MS patients. J Neurol. 2014;261:1170-1177.
16. Vellinga MM, Castelijns JA, Barkhof F, Uitdehaag BM, Polman CH. Postwithdrawal rebound increase in T2 lesional activity in natalizumab-treated MS patients. Neurology. 2008;70:1150-1151.
17. Giovannoni G, Turner B, Gnanapavan S, Offiah C, Schmierer K, Marta M. Is it time to target no evident disease activity (NEDA) in multiple sclerosis? Mult Scler Relat Disord. 2015;4:329-333
18. Banwell B, Giovannoni G, Hawkes C, Lublin F. Editors' welcome and a working definition for a multiple sclerosis cure. Mult Scler Relat Disord. 2013;2:65-67.
19. Perumal J, Balabanov R, Su R, Chang R, Balcer L, Galetta S, Campagnolo DI, Avila R, Lee L, Rutledge D, Fox RJ. Natalizumab in Early Relapsing-Remitting Multiple Sclerosis: A 4-Year, Open-Label Study. Adv Ther. 2021;38:3724-3742.
20. Diem L, Nedeltchev K, Kahles T, Achtnichts L, Findling O. Long-term evaluation of NEDA-3 status in relapsing-remitting multiple sclerosis patients after switching from natalizumab to fingolimod. Ther Adv Neurol Disord. 2018;11:1756286418791103.
21. Kalincik T, Sharmin S, Roos I, Freedman MS, Atkins H, Burman J, Massey J, Sutton I, Withers B, Macdonell R, Grigg A, Torkildsen Ø, Bo L, Lehmann AK, Havrdova EK, Krasulova E, Trnený M, Kozak T, van der Walt A, Butzkueven H, McCombe P, Skibina O, Lechner-Scott J, Willekens B, Cartechini E, Ozakbas S, Alroughani R, Kuhle J, Patti F, Duquette P, Lugaresi A, Khoury SJ, Slee M, Turkoglu R, Hodgkinson S, John N, Maimone D, Sa MJ, van Pesch V, Gerlach O, Laureys G, Van Hijfte L, Karabudak R, Spitaleri D, Csepany T, Gouider R, Castillo-Triviño T, Taylor B, Sharrack B, Snowden JA; MSBase Study Group Collaborators; MSBase Study Group Authors; Mrabet S, Garber J, Sanchez-Menoyo JL, Aguera-Morales E, Blanco Y, Al-Asmi A, Weinstock-Guttman B, Fragoso Y, de Gans K, Kermode A; MSBase Study Group. Comparative Effectiveness of Autologous Hematopoietic Stem Cell Transplant vs Fingolimod, Natalizumab, and Ocrelizumab in Highly Active Relapsing-Remitting Multiple Sclerosis. JAMA Neurol. 2023;80:702-713.
22. Prosperini L, Fanelli F, Pozzilli C. Long-term assessment of No Evidence of Disease Activity with natalizumab in relapsing multiple sclerosis. J Neurol Sci. 2016;364:145-147.