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Detection Barriers of Multiple Sclerosis on Disease Progression & Management: A Systematic Review

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Abstract

A systematic review of the literature was conducted to examine the independent barriers and clinical implications of delaying the detection and multifaceted treatment of Multiple Sclerosis (MS). Further, the significance of detecting neurocognitive impairments to inform diagnosis and monitor decline as the disease progresses was explored. An in-depth qualitative analysis was performed to appraise the collected research and establish generalizability of homogenous findings across studies. Findings suggest that the heterogenous makeup of MS serves as the predominant barrier in obtaining subclinical or an early definite diagnosis, with earlier initiation of disease-modifying treatments (DMTs) exhibiting long-term benefits in patients with relapse-remitting subtypes (Schwenkenbecher et al., 2019; Eccles, 2019; Miller, 2004; Rolak, 2003; Waubant, 2012). The greatest occurrences of diagnostic errors were reported across numerous studies to have been induced by misinterpretation of MRI lesions, atypical clinical manifestations, and inaccurate determination of alternate conditions due to congruent CNS presentations (Solomon et al., 2016; Calabrese et al., 2019; Schwenkenbecher et al., 2019; Rolak, 2003). Several studies indicated that early detection of cognitive decline via the administration of screenings in the initial work-up and post-onset may assist in informing diagnosis, determining eligibility for participation in neurocognitive trainings, and properly allocating psychological resources as needed (Foley et al., 2012; Kalb et al., 2018; Islas & Ciampi, 2019; Oreja-Guevara et al., 2019).

Introduction

Multiple Sclerosis (MS), a chronic and progressive inflammatory neurodegenerative autoimmune disease characterized by demyelination of the neuronal axons, grey matter lesions, and cortical atrophy within the central nervous system (CNS), is the predominant cause of neurological disability among young adults aged 20 to 40 years of age (National Institute of Neurological Disorders and Stroke, 2020). The highest rates of onset of MS are prevalent in adults, with approximately less than 1% being detected in childhood and 2-10% being detected in the elderly (Ghasemi et al., 2017). There are four main subtypes of MS that have been identified and characterized based on their distinctive features: relapse-remitting (most common form),

secondary progressive, primary progressive, and progressive-relapsing (rarest) (National Institute of Neurological Disorders and Stroke, 2020). The disease course and clinical progression directly correlate to the specific subtype of MS that the patient acquires, with higher incidences of irreversible disability presenting in the primary progressive and progressive-relapsing forms (Ontaneda & Fox, 2015; John Hopkins Medicine, 2020; Cedars Sinai, 2019; Goldenberg, 2012).

The exact etiology of MS currently remains in question due to the heterogenous makeup of its presentation and lack of specific biomarkers that dictate its triggers; however, the pathological markers involved in its onset and progression have been globally identified as a T cell mediated autoimmune inflammatory condition, with predominant involvement of the CD8+ T cells (Huang et al., 2017; Ghasemi et al., 2017). A cardinal aspect of MS consists of white matter plaque formations across the ventricles, optic nerve, and corpus callosum, with a number of patients simultaneously presenting with grey matter atrophy (Huang et al., 2017; Ghasemi et al., 2017). Reduced oligodendrocytes, oligodendrocyte apoptosis, astrocyte proliferation with gliosis, and perivascular and parenchymal infiltrates of lymphocytes and macrophages further serve as evidenced neurological markers in the presentation of MS (Huang et al., 2017; Ghasemi et al., 2017).

Relapse-remitting MS (RRMS) comprises approximately 85% of cases, with its identifying features consisting of sudden onset of episodes followed by complete or partial remission of symptoms (Lublin et al., 2014; Goldenberg, 2012). Pathological indications of RRMS suggest patterns of T cell mediated axonal injury, high levels of inflammatory plaques, and attacks on the myelin sheath presenting on neuronal magnetic resonance imaging (MRI) (Lublin et al., 2014; Goldenberg, 2012). In the absence of DMTs, approximately 50% of patients with RRMS will develop secondary progressive MS (SPMS) within 10 years post-onset, evidenced by the presentation of progressive neurological decline following initial relapses, independent of remissions (Gross & Watson, 2017; Goldenberg, 2012; Dutta & Trapp, 2014). Pathological indicators of SPMS suggest patterns of high cortical and white matter lesions, abundant subpial lesions, and diminished neuronal repair capacity within the brain as seen on MRI (Gross & Watson, 2017; Goldenberg, 2012; Dutta & Trapp, 2014).

Approximately 10% of patients will acquire primary progressive MS (PPMS), which has been found to be associated with a higher risk of permanent disability due to the characteristic gradual progression of the disease without any remission, thus indicating a poorer prognosis, particularly in patients presenting with acute myelopathy early-on in the disease course (Ontaneda & Fox, 2015; John Hopkins Medicine, 2020). Primary pathological indicators of PPMS on MRI consist of prominent brain atrophy, spinal cord atrophy, cortical lesions, and limited inflammatory plaques, functionally presenting as myalgia, neuralgia, electric-shock sensations, ambulatory deficits, and potential paralysis (Ontaneda & Fox, 2015; John Hopkins Medicine, 2020). Limited research exists regarding the least common form of MS, progressive-relapsing MS (PRMS), presenting in less than 5% of reported cases (Cedars Sinai, 2019; Goldenberg, 2012). The pathological indicators of PRMS mimic the biomarkers found in PPMS, with the chief distinction being the onset of relapses associated with worsening of symptoms as the disease gradually progresses (Cedars Sinai, 2019; Goldenberg, 2012).

Biomarker specificity limitations for MS reduce the diagnostic precision, thus a confirmed diagnosis relies on the amalgamation of various tests and ultimately, the providing physician's clinical judgment (Ford, 2020; Mantero et al., 2018; Schwenkenbecher et al., 2019). Obtaining a diagnosis of MS involves the collection of a patient's medical history to evaluate presenting symptoms, a neurological examination to assess cranial nerve function, MRI/CT imaging to detect

lesions, lumbar punctures primarily for analyzing cerebrospinal fluid concentrations (CSF), blood sample analyses, and exclusion of all other potential diagnoses (Ford, 2020; Mantero et al., 2018; Schwenkenbecher et al., 2019). Evoked potential tests may be utilized to evaluate nerve conduction in efforts to identify slowed, obstructed, impaired saltatory, and interrupted conduction; however, lesions within the deep cortical structures of the brain may be undetected, thus this method serves as a supportive tool (Ford, 2020; Mantero et al., 2018; Schwenkenbecher et al., 2019). Primary clinical markers of the disease that shape the diagnostic criteria for MS consist of the presentation or history of a clinically isolated syndrome (CIS), CSF positive for oligoclonal bands, the presence of 1 or more lesions in at least 2 distinct areas of the central nervous system (CNS) or dissemination in space (DIS), and lesions distinguishable on MRI imaging on 2 separate occasions or dissemination in time (DIT) (Goldenberg, 2012; Schwenkenbecher et al., 2019).

Clinical manifestations of MS vary on patient-by-patient basis, and tend to generalize to the specific subtype of disease, with chief complaints ranging from visual disturbance to spinal cord weakness (Ghasemi et al., 2017; Solomon et al., 2019). Symptom presentations of the disease may consist of mild unilateral optic neuritis with partial or full recovery, facial sensory loss, fatigue, trigeminal neuralgia, cerebral syndromes (i.e., ataxia, nystagmus, tremor), sensory disturbances (i.e., paresthesia, itching), localized spinal cord weakness, limb weakness or numbness, urinary incontinence, bladder dysfunction, dysphagia, dysarthria, seizures, headaches, and cognitive deficits (Ghasemi et al., 2017; Solomon et al., 2019).

Neurocognitive deficits have been reported to be one of the earliest clinical indicators of MS, with some evidence indicating they may present prior to observation of MRI structural lesions (Kalb et al., 2018; Islas & Ciampi, 2019; Oreja-Guevara et al., 2019). Prominent domains affected by cognitive decline may be comprised of, but not limited to, slowed information processing speed (evident in approximately 40-70% of patients), executive functioning deficits (evident in approximately 15-25% patients), memory deficits (evident in approximately 40-65% of patients), complex attention difficulties (evident in approximately 20-50% of patients), and social cognitive impairments, particularly in facial emotional recognition (evident in approximately 20% of patients) (Kalb et al., 2018; Islas & Ciampi, 2019; Oreja-Guevara et al., 2019).

Despite the substantial impact cognitive decline has on patients' physical and mental well-being, limited attention has been directed at properly screening for or monitoring said changes as the disease progresses (Kalb et al., 2018; Islas & Ciampi, 2019; Oreja-Guevara et al., 2019). One survey study found that approximately 49% of healthcare professionals did not have any objective screening procedures to assess neurocognitive functioning, despite the moderate-high counts of MS patients presenting with cognitive decline (Foley et al., 2012). According to numerous studies, neurocognitive decline has been associated with a diminished quality of life, poorer adherence to treatments, reduced rates of employment, lower income, impaired ADL's, impaired driving capacity, and higher levels of reported caregiver burden for family members (Kalb et al., 2018; Islas & Ciampi, 2019; Oreja-Guevara et al., 2019).

MS risk factors may be classified by genetic and proposed environmental factors that serve as triggers or precipitators of the disease found in numerous groups of patients (Waubant et al., 2019; Ghasemi et al., 2017). As per selective MS studies, the monozygotic risk rate averages approximately 25%, while the dizygotic and first-degree relative risk rate substantially decreases to approximately 2-5% (Waubant et al., 2019; Ghasemi et al., 2017). With globally-expanding research continuing to be conducted to accurately depict MS-specific biomarkers, a link between the human leukocyte antigen (HLA) class II and T cell mediated CNS destruction has been

repeatedly observed in the initial and progressive phases of the disease (Waubant et al., 2019; Ghasemi et al., 2017). Potential environmental risk factors have been identified, one of which includes exposure to viral and bacterial infections, with highest associations having been found in patients with a past medical history of the Epstein-Barr Virus (EBV) (with an almost 100% antibody positivity rate) (Waubant et al., 2019; Ghasemi et al., 2017). Some evidence has linked the occurrence of MS to high levels of exposure to neurotoxins, specifically nicotine, as well as vitamin D and B12 deficiencies in geographic domains with limited sun exposure (Waubant et al., 2019; Ghasemi et al., 2017).

Methods

The aim of this systematic review was to gain insight into the distinctive barriers affiliated with the detection of MS in efforts to enhance awareness of clinical implications associated with delaying treatment. Further, this review explored the significance of detecting neurocognitive changes presenting in patients, as well as in utilizing screeners to evaluate declines across various stages of the disease. Research collection was derived from electronic databases, online national health department resources, and private U.S.-based health institutions consisting of PubMed, National Institutes of Health (NIH), National Library of Medicine (NLM), Centers for Disease Control and Prevention (CDC), National Institute of Neurological Disorders and Stroke (NINDS), Cedars-Sinai Health Library, and Johns Hopkins Medicine. The data were extracted from randomized clinical control trials, longitudinal studies, cross-sectional studies, multicenter studies, statistical reports, health surveys, population-based surveys, administrative data sets, systematic reviews, meta-analytic reviews, regulatory reviews, and self-report questionnaires from the years 2000 to 2020.

Inclusion criteria consisted of national/international research conducted in inpatient/outpatient hospital settings, community health centers, academic health centers, or health institutions. The population of the studies included in this review were participants/patients aged 16 and over who either have a definite diagnosis of adult-onset MS, are suspected to have MS, are at risk for developing MS, or are presenting with symptoms mimicking MS. Excluded articles were those with participants/patients who currently have or have been diagnosed with pediatric-onset MS, non-peer reviewed studies, and observational studies utilizing qualitative methodologies.

Risk of bias was addressed by incorporating studies with randomized selection for intervention vs. control groups, mostly larger sample sizes to increase external validity, and reported outcomes utilizing quantitative measures to analyze the data.

Detection Barriers of Multiple Sclerosis

Neurologically-induced somatic manifestations of MS mimicking alternate diseases, rapid relapse-remitting symptom onset, patient apprehension in initially consulting with a physician, and the variable clinical/observational tests required to constitute a diagnosis partially contribute to the hinderance of early detection, thus resulting in a delay in treatment (NINDS, 2020; Rolak, 2003; Waubant, 2012; Noyes & Weinstock-Guttman, 2013). One health survey study conducted by Solomon et al., 2016, collected patient data from 23 neurologists at 4 different U.S. academic medical centers (i.e., Mayo Clinic, University of Vermont, Oregon Health and Science University, Washington University) for 93 females and 17 males between the ages of 21 to 77 years who had been misdiagnosed (Solomon et al., 2016). Among the 110 misdiagnosed patients, 51 were given “definite” misdiagnoses, while 59 were given “probable” misdiagnoses. Of the misdiagnosed

patients, 22% were given a diagnosis of migraine alone or with other conditions, 15% were given a diagnosis of fibromyalgia, 12% were given a diagnosis of non-specific or non-localizing neurological symptoms with an abnormal MRI, 11% were given a diagnosis of conversion or psychogenic disorders, and 6% were given a diagnosis of neuromyelitis optica spectrum disorder (Solomon et al., 2016).

The study found that primary factors contributing to the misdiagnosis consisted of misinterpretation of the MRI findings, inaccurate determination of the locations of specific lesions, inconclusive objective evidence of demyelinating historical events, and misinterpretation of reported symptoms associated with relapse episodes (Solomon et al., 2016). Limitations of this study include insufficient reporting of misdiagnosed patients in proportion to the correctly diagnosed patients, lack of identification of the criteria utilized to guide the diagnoses at the medical centers, as well as lack of symptom report profiles for the patients presenting at the initial point of diagnosis.

Another longitudinal study assessing the clinical indicators of an MS diagnosis and alternate diagnosis included 667 participants averaging 40.6 years of age, from 22 various MS centers across Italy who were in need of a diagnostic work-up (Calabrese et al., 2019). Patients with an established diagnosis of MS were excluded from the study to reduce quality interference of the data. Participants were divided into 2 main groups, ones with suggestive symptoms and ones with suggestive atypical presentations of MS. A clinical and radiological diagnostic work-up was conducted at baseline, and at 3-year follow-ups, which analyzed MRI's of the brain and spinal cord, CSF concentrations, and blood samples.

Through the implementation of a multivariate analysis, the results of the study found that 24.6% of the participants did not meet criteria for MS, but rather had been clinically assigned a diagnosis of non-specific neurological symptoms due to abnormal MRI findings with suspected vascular origin (n=40), migraine with atypical lesions (n=24), neuromyelitis optica (n=14), and other syndromes mimicking MS (e.g., chronic inflammatory demyelinating polyneuropathy, systemic lupus erythematosus, etc.) (Calabrese et al., 2019). Approximately 60.1% were diagnosed with MS utilizing the McDonald 2017 criteria, and the few remaining participants had been assigned a CIS (Calabrese et al., 2019). According to this study, independent predicters of being assigned an alternate diagnosis consisted of, but were not limited to, negative oligoclonal bands in the CSF, abnormal presenting lesions on MRI, absence of DIS, and normal evoked potential tests (Calabrese et al., 2019). Limitations to note in this study were the lack of reported subtypes of MS that had been evaluated for diagnosis or exclusion, as well as the inability to obtain data regarding the accuracy of the alternate diagnoses assigned post the 3-year follow-up.

Determining the most suitable criteria to utilize in guiding diagnostic precision may prompt heterogenous outcomes in MS screenings for patients presenting with typical and atypical clinical features. A systematic review conducted by Schwenkenbecher et al. (2019), evaluated the impact the updated McDonald 2017 criteria had on early detection and diagnosis across 8 international studies. Marked findings of the review focused on the significance of performing CSF analyses to screen for the presence or absence of oligoclonal bands, abnormal protein concentrations, neutrophils, eosinophils, or alternate atypical cells that may serve as indicators of the disease or of an alternate condition (Schwenkenbecher et al., 2019).

Further, in accordance with the updated version of the McDonald criteria, a positive test for oligoclonal bands may substitute the requirement for DIT in obtaining an MS diagnosis due to its increased predictive value of the disease presenting in the majority of patients (Schwenkenbecher et al., 2019). The study noted that oftentimes patients may initially obtain a

negative test for oligoclonal bands; thus, re-assessment is recommended to confirm the absence or presence of the immunoglobulin proteins considering the increased rates of positive tests upon re-analysis (Schwenkenbecher et al., 2019). A few studies evaluated as part of the systematic review failed to retrieve MRI data for all patients screened. In addition, the McDonald criteria were utilized in a number of patients after receiving an MS diagnosis, thus limiting the measure of impact it had on the process of initially detecting the disease (Schwenkenbecher et al., 2019).

Timing of Treatment on Disease Progression

Collective detection barriers of MS are noted to produce delayed identification of the presence of the disease, thus prolonging the vital implementation of DMTs to assist in mitigating acute and chronic relapses. A clinical trial conducted by Comi et al. (2012) as part of a multicenter phase 3 study randomly assigned 515 patients aged 18-50 years to one of three groups in efforts to evaluate the clinical implications of applying pre-mature pharmacological treatment to patients presenting with symptoms suggestive of MS, who have not yet obtained a definite diagnosis. Participants screened must have met the inclusion criteria of having had a history of a single clinical event, and at least two silent T2 brain lesions presenting on MRI. In addition, individuals with a diagnosis of MS, major medical or psychiatric history, current autoimmune disease, history of alcohol or substance abuse, or moderate to severe renal impairment were excluded from the study (Comi et al., 2012). Participants were randomly assigned to either a group receiving subcutaneous interferon beta-1a 44 μg 3x/week + placebo 2x/week for up to 24 months, a group receiving subcutaneous interferon beta-1a 44 μg 1x/week + placebo 2x/week for up to 24 months, or a placebo group 3x/week for up to 24 months (Comi et al., 2012).

At the 2-year mark, participants who received subcutaneous interferon beta-1a 44 μg 3x/week and 1x/week exhibited a significantly lower probability of obtaining an MS diagnosis compared to placebo ($p<0.0001$; $p=0.008$) (Comi et al., 2012). Furthermore, at the 2-year mark, participants who received subcutaneous interferon beta-1a 44 μg 3x/week and 1x/week exhibited a significantly lower rate of conversion to MS compared to placebo ($p=0.0004$; $p=0.0023$) (Comi et al., 2012). These findings are suggestive of the clinical significance in detecting and initiating pharmacological treatment during the prodromal phases of the disease as a means of prolonging onset and diminishing rates of conversion (Comi et al., 2012). Of note, this clinical trial was not inclusive of participants with atypical MRI lesions indicative of MS, thus, generalizability to patients presenting with abnormal clinical manifestations remains low. Additionally, long-term clinical assessment of the participants did not exceed 2 years, therefore, the timing or absence of onset of the disease after the follow-up mark could not be determined. Future clinical trials evaluating long-term effects of treatment initiation on disease modification or delay should consider prolonging follow-up assessments to greater time gaps in efforts to solidify the findings.

A longitudinal study by Chalmer et al. (2018) was conducted to evaluate the clinical efficacy of implementing treatment at various times of the disease course on the development of disability among 3,795 patients recruited from two nation-wide population-based MS registries. Participants were separated into either the early treatment group (i.e., within 2 years of symptom onset), or the late treatment group (i.e., within 2-8 years post-symptom onset); the expanded disability status scale (EDSS) was utilized to measure the degree of disability (Chalmer et al., 2018). According to the study's findings, the late treatment group exhibited a 42% increased risk rate of obtaining an EDSS score of 6 (i.e., identifying significant disability), compared to the early treatment group ($p<0.001$) by the approximate 7-year mark (Chalmer et al., 2018). At the 10-year mark, the late treatment group was found to have a 38% increased mortality rate, indicating a

potential poorer prognosis for MS patients having obtained treatment further into the disease course.

A 12-year longitudinal study conducted by Dekker et al. (2019), utilized presenting MRI structural abnormalities and neuropsychological test results to highlight predictors of disability and cognitive decline in patients with varying subtypes of MS. Participants recruited from an Amsterdam early inception cohort consisted of 76 females and 36 males with a mean age of 35.3; the baseline diagnoses that were assigned in accordance to the McDonald criteria of 2005 were comprised of 36 individuals with CIS, 68 with RRMS, and 11 with PPMS (Dekker et al., 2019). Level of disability was measured via the EDSS; cognitive functioning was assessed via the Brief Repeatable Battery of Neuropsychological Tests (BRB-N). The study found that higher EDSS scores (i.e., greater degrees of disability) at the 6-year mark were predicted by earlier EDSS scores, whole-brain volume changes, and a baseline diagnosis of PPMS (Dekker et al., 2019). Higher EDSS scores at the 12-year mark were found to be predicted by greater EDSS score changes and T1-hypointense lesion volumes on MRI (Dekker et al., 2019).

Findings regarding cognitive changes at the 6-year mark were predicted by a baseline diagnosis of PPMS, lower level of education, being male, and earlier whole-brain atrophy, while at the 12-year mark, predicters included lower level of education, being male, and having greater baseline T1-hypointense lesion volumes on MRI (Dekker et al., 2019). Lower levels of education were solely associated with increased cognitive decline as the disease progressed, potentially reflecting the long-term benefits of cognitive reserve (Dekker et al., 2019). Due to the primary evaluation of PPMS subtypes, representing a typically rarer form of MS, generalizability to the majority of diagnosed patients could not be attained based on the results of this reported study. Thus, further assessments of the most common diagnosed subtype (i.e., RRMS) are recommended to strengthen its scientific contribution.

Cognitive Manifestations of the Disease

Cognitive deficits have been noted across studies as one of the earliest indicators of MS, with some evidence demonstrating clinical onset of changes in functioning prior to the presentation of structural MRI abnormalities (Kalb et al., 2018; Islas & Ciampi, 2019; Oreja-Guevara et al., 2019). A cross-sectional study conducted by Achiron et al. (2013) to assess patterns of cognitive impairment in MS patients with a disease duration of up to 30 years collected data for 1,500 patients at an MS center at the Sheba Medical Center in Israel. The demographic profile of the registered patients included individuals aged 18-65 years, with 200 diagnosed with a CIS, 1,173 with RRMS, 100 with SPMS, and 27 with PPMS. Individuals having received corticosteroid treatment within 3 months of the start of the study were excluded, along with those with an indicated history of psychiatric illness and/or alcohol/drug abuse (Achiron et al., 2013). The investigators in the study utilized the Mindstreams Global Assessment Battery (GAB), a 45-minute computerized neuropsychological test measuring information processing speed, verbal functioning, and visuospatial processing.

Results of the study revealed that MS patients performed significantly lower on global cognitive testing than healthy controls, with all subtypes exhibiting cognitive decline within 5 years of disease onset (Achiron et al., 2013). SPMS patients exhibited higher levels of cognitive impairment than CIS patients ($p<0.0001$), and performed significantly poorer than RRMS and PPMS patients on all cognitive domains with the exception of visuospatial functioning ($p<0.0001$) (Achiron et al., 2013).

A study conducted by Staff et al. (2009) evaluated the clinical presentations of 23 patients from the Mayo Clinic who have been diagnosed with either RRMS (9), PPMS (11), or SPMS (3), with the primary disabling neurological symptom of severe cognitive impairment. The patients' cognitive functioning were evaluated utilizing the Kokmen Short Test of Mental-Status, a 38-point screener typically administered to assist in diagnosing mild cognitive impairment (MCI), Alzheimer's Disease (AD), or alternate forms of dementia. In reference to the diverse data collected on the MS patients, the median age of onset of CNS demyelination was 33 years, while the median age of onset of cognitive impairment was 39 years (Staff et al., 2009). Of the 23 patients, 17 exhibited cognitive deficits at onset, 14 were reported to experience progressive declines that led to disability, and 9 were reported to have experienced acute onset of cognitive dysfunction associated with spontaneous attacks (Staff et al., 2009). The wide majority of patients (i.e., 95%) expressed CSF abnormalities, 13 presented with mild cerebral ataxia, and 15 presented with comorbid psychiatric disturbances (i.e., depression, psychotic features) (Staff et al., 2009). The small sample size of the study, the lack of specificity of the cognitive screener utilized to assess impairments, and the absent data collected on the clinical manifestations of patients immediately following a CIS collectively and independently hinder generalizability to similar populations, necessitating further research .

Neuropsychological Measures as Clinical Tools for Evaluating Decline

With cognitive deficits being one of the earliest prominent features of MS, identifying screening measures of high sensitivity and specificity appears to be an on-going challenge in a multitude of health settings (Foley et al., 2012; Kalb et al., 2018; Islas & Ciampi, 2019; Oreja-Guevara et al., 2019). There is currently insufficient implementations of formal, standardized screenings to be utilized as part of either the diagnostic work-up to inform detection, or to be routinely administered post-onset as an objective means of monitoring changes (Foley et al., 2012; Kalb et al., 2018; Islas & Ciampi, 2019; Oreja-Guevara et al., 2019).

A study conducted by Kim et al. (2017) recruited 100 participants (75 females, 25 males), aged 18-77 years from an MS clinic in New Jersey to evaluate the efficacy of the utility of specified cognitive measures as a method of detecting preliminary declines. The participants had been diagnosed with either RRMS (n=88), PPMS (n=5), or SPMS (n=7), with a mean level of education of 14.51 years. The assessments utilized in the study were the Minimal Assessment of Cognitive Function in MS (MACFIMS) and the Symbol Digit Modalities Test (SDMT) (administered independently and as part of the MACFIMS) (Kim et al., 2017). In efforts to assess behavioral, emotional, and neuropsychological functioning from a subjective perspective, patients were instructed to complete the Multiple Sclerosis Neuropsychological Screening Questionnaire-Patient Version (MSNQ-P), the Behavior Rating Inventory of Executive Function-Adult version (BRIEF-A), the Problem-Solving Inventory, and the Beck Depression Inventory, 2nd Edition (BDI-II) (Kim et al., 2017). The study reported that the SDMT performed better than the MACFIMS at distinguishing between patients who did not exhibit cognitive impairments. The SDMT, utilized independently, was found to be the greatest predicter of cognitive impairment, with a classification accuracy of 89%, sensitivity of 69%, and specificity of 90.8% (Kim et al., 2017). Further, higher levels of depression were associated with increased levels of subjectively reported cognitive decline; however, no significant correlations were found on objective testing, evidencing the indirect effects of emotional functioning on perceived cognitive abilities (Kim et al., 2017).

A systematic review conducted by Islas & Ciampi (2019), simultaneously reported that the SDMT demonstrated highest rates of sensitivity (mean of approximately 82%), good specificity

(mean of approximately 60%), and good to excellent reliability across studies in detecting and monitoring cognitive decline, exclusively for information processing speed (i.e., the predominantly affected cognitive domain in patients with MS). The review found that the most frequently utilized neurocognitive batteries in assessing cognitive functions were comprised of the BRB-N, the MACFIMS, and the Brief International Cognitive Assessment for MS (BICAMS) (Islas & Ciampi, 2019).

Another study conducted by Hansen et al. (2015) evaluated the psychometrics of the shortened version of the BRB for measuring cognition in MS patients. The investigators recruited 127 participants (85 females, 42 males) diagnosed with MS, aged 18-75 years from the Department of Neurology in Klinikum Bayreuth, Germany. The specific assessments selected to be administered from the extended battery consisted of the California Verbal Learning Test (CVLT), the Test of Attentional Performance (TAP), the Weschler Memory Scale-Revised (WMS-R), the Five-Point Test (FPT), and the Regensburger Wortschatz Test (RWT). Assessments selected from the shortened battery consisted of the Selective Reminding Test (SRT), the SDMT, and the Paced Auditory Serial Addition Test (PASAT). According to the study, cognitive deficits were objectively observed in 72 patients who completed the extended battery, and 75 patients who completed the shortened battery (Hansen et al., 2015). The SRT, SDMT, and PASAT demonstrated a a 77.8% sensitivity rate and 64.8% specificity rate when utilized collectively to assess cognition, with the SDMT revealing the highest specify rate at 89.47% when administered as an independent measure (Hansen et al., 2015).

Neurorehabilitation on Cognitive Performance

Incorporating routine cognitive screenings in addition to analyzing the data to select measures with the highest evidence of enhanced efficacy in detecting and monitoring decline are marked to be a few of the challenges in the diagnosis and long-term management of MS. With cognitive impairment being identified as one of the chief complaints that patients report, as well as a noted reducer of quality of life, it is evident that post-detection of the deficits, and evaluating modes of treatment in combatting the decline, would be the succeeding priority.

In a multicenter observational study conducted, Barbarulo et al. (2018) sought to determine the efficacy of integrating cognitive and neuromotor rehabilitation to improve patient functioning. Participants with a mean education level of 14.24, aged 23-65 years, were recruited from two Italian medical centers (n=63), with 9 diagnosed with RRMS and 54 diagnosed with PPMS. Individuals with a history of or current major psychiatric illness, alternate neurological disorder, history of head trauma, learning disability, or alcohol/drug abuse were excluded from the study. Participants were assigned to either the integrated treatment group, which included cognitive and neuromotor rehabilitation, or the motor treatment group, which solely included the neuromotor rehabilitation (Barbarulo et al., 2018). Treatment was conducted for both groups over two 60-minute sessions per week for 24 weeks, with the BRB utilized to measure cognitive functioning.

As per the study's report, the integrated treatment group exhibited significant improvements on nine of the neuropsychological tests within the BRB, consisting of spatial span (p=0.003), forward verbal span (p=0.032), backward verbal span (p=0.027), phonological fluency (p<0.001), frontal assessment battery (p=0.009), Barthel index modified (p=0.016), Tinetti balance scale (p<0.001), Tinetti gait scale (p=0.027), and Tinetti overall scale (p<0.001), while the motor treatment group demonstrated significant improvements on two of the neuropsychological tests, including world list generation (p=0.030) and selective-reminding test delayed (p=0.031) (Barbarulo et al., 2018). Participants presenting with comorbid autoimmune conditions, metabolic,

or endocrine disorders that may simultaneously impact neurocognitive and motor functioning were not excluded from the study; thus, overlap of MS-induced decline may have occurred. Further, the majority of participants in the study were diagnosed with PPMS, a rarer form of MS that tends to induce greater levels of cognitive impairment and rates of disability than the most common form.

A randomized control study conducted by Pérez-Martín et al. (2017) evaluated the efficacy of implementing a computer-assisted cognitive training program to improve functioning in 62 MS patients. Patients with a current or previous history of severe psychiatric illness, met criteria for dementia, obtained less than a 24 on the Mini Mental Status Examination (MMSE), or that had received corticosteroid treatment within 3 months of the start of the study were excluded from participation. Participants diagnosed with either RRMS (*n*=57), SPMS (*n*=2), or PPMS (*n*=3), were recruited from the University Hospital of the Canary Islands and the José Molina Orosa Hospital in Spain (Pérez-Martín et al., 2017). Participants were assigned to either the intervention group or control group; the intervention group received 60-75 minutes of cognitive training for 12 weeks and were administered the BRB, MSNQ, Fatigue Severity Scale (FSS), Hospital Anxiety and Depression Scale (HADS), and Multiple Sclerosis Quality of Life-54 (MSQoL-54) (Pérez-Martín et al., 2017).

The study's reported findings identified the intervention group as having demonstrated significant improvements on four of the neuropsychological tests within the BRB (i.e., PASAT, SRT, special recall test, and controlled oral word association test), while no significant improvements were observed in the controls (Pérez-Martín et al., 2017). Further, in regard to subjective behavioral and emotional functioning, significant improvements were noted on the HADS, MSNQ, and MSQoL-54. (Pérez-Martín et al., 2017). Due to the evaluation of the cognitive training program having been exclusively computerized, expanding the data via incorporating non-computerized training modalities would benefit the field and enhance the available quantitative research on the role of implementing non-pharmacological treatments to inhibit or slow the rate of decline in these populations.

Discussion

The neuropathological heterogeneity, vast clinical presentations, and highly intricate makeup of MS has prompted the rise of on-going data revisions regarding the mechanisms involved in its development and progression (Gelfand, 2014). MS has been discovered to be a T cell mediated, chronic autoimmune neurodegenerative condition, prompting widespread CNS atrophy, and is induced by the infiltration of the blood-brain barrier (BBB), demyelinated axons, inflammatory plaques, glial injury, oligodendrocyte apoptosis, etc. (Huang et al., 2017; Cortese et al., 2019). Delayed detection of MS resulting from its unpredictable, incongruous clinical presentation and lack of identified contributable biomarkers hinders premature or early diagnosis, thus evoking a lapse in the initiation of DMTs (Waubant, 2012; Rolak, 2003; Noyes & Weinstock-Guttman, 2013; Miller, 2004).

Homogenous early detection barriers of MS have been recognized by numerous researchers over the years, with the vast majority of studies reporting increased occurrences of misinterpreted MRI lesions, atypical physiological and somatic presentations, and misdiagnosis of CNS conditions mimicking the disease as being the chief culprits (Solomon et al., 2016; Calabrese et al., 2019; Schwenkenbecher et al., 2019; Rolak, 2003). Misinterpretation of MRI lesions have been reported to be partially provoked by the low-specificity of the noted atrophy, inaccurate determination of juxtacortical and periventricular lesion locations, oligoclonal bands presenting in alternate inflammatory conditions, non-distinguishable cortical lesions, distinct neurological

symptoms, and imaging findings failing to correlate with the patient's clinical presentation (Solomon et al., 2016; Calabrese et al., 2019; Eccles, 2019; Miller, 2004; Rolak, 2003). Growing incidences of diagnostic errors among these populations have elicited adverse outcomes, with the highest rates occurring in patients with non-specific or non-localizing neurological symptoms with abnormal MRIs, fibromyalgia, migraine with abnormal MRIs, and neuromyelitis optica spectrum disorder (Solomon et al., 2016; Calabrese et al., 2019; Schwenkenbecher et al., 2019). Further, rapid relapse-remitting onset, patient apprehension in undergoing a lumbar puncture, initial resistance in consulting with a physician, heavy reliance on clinical judgement to constitute a diagnosis, and non-specific pathological laboratory findings may hinder prompt detection, thus delaying implementation of treatment (NINDS, 2020; Rolak, 2003; Waubant, 2012; Noyes & Weinstock-Guttman, 2013).

To assist in enhancing the detection accuracy and decrease disease misinterpretations, the criteria utilized to guide diagnosis (i.e., McDonald criteria) underwent adjustments in 2017, with the most noteworthy one being that a positive oligoclonal band test may be substituted for DIT (Schwenkenbecher et al., 2019). These updated revisions to the medical guidelines restrict the need for follow-up MRIs to be conducted to confirm activation of lesions on two separate occurrences, thus, narrowing the risk of diagnostic errors and inaccurate dissection of the imaging (Schwenkenbecher et al., 2019). Early detection barriers inevitably produce delayed initiation of DMTs, adversely affecting disease prognosis and patient outcomes (Waubant, 2012). Numerous clinical trials evaluating the long-term effects of DMTs have reported a significant reduction in the probability of developing MS, lower rates of conversion to MS, and a decrease in the occurrence of relapses in RRMS patients (Comi et al., 2012; Waubant, 2012; Rolak, 2003). DMTs have additionally been observed to prolong the progression into permanent disability and reduce mortality rates of patients when treated within two years post-onset of symptoms (Chalmer et al., 2018; Waubant, 2012; Rolak, 2003). The significance of administering treatment during the early stages of the disease is essential to maintaining the effectiveness of DMTs, especially with studies reporting diminished efficacy once RRMS has progressed into secondary progressive forms (Waubant, 2012; Rolak, 2003). Increased risk of irreversible disability, delayed symptom management, and prolonged psychological distress induced by unexplainable, somatic discomfort serve as attributable factors to untimely distribution of treatment (Waubant, 2012; Rolak, 2003).

Distinctive aspects of the physiological makeup, clinical presentation, and external features of MS have been identified as potential predictors of the progression of the disease. Delayed detection, misdiagnosis, and delayed treatment have been reported by studies to contribute to negative long-term outcomes, particularly in patients with RRMS subtypes who have demonstrated enhanced benefits from receiving DMTs early-on (Alroughani et al., 2015; Dekker et al., 2019; Solomon & Corboy, 2017; Kalb et al., 2018). Early onset of cognitive impairments, premature disability, spinal cord and/or global brain atrophy at onset, higher T1-hypointense lesion volumes observed on MRI, a diagnosis of PPMS, and the development of MS at an age greater than 40 have been reported to elicit a poorer prognosis (Alroughani et al., 2015; Dekker et al., 2019; Solomon & Corboy, 2017; Kalb et al., 2018; Achiron et al., 2013).

Neurocognitive manifestations of MS may be exhibited early in the course of the disease, evidencing the need for timely and accurate recognition of changes to ensure proper allocation of resources, improve patient safety, enhance management of adverse behavioral effects, initiate cognitive trainings, and elicit the need for placement in neurorehabilitation centers among patients with advanced decline (Foley et al., 2012; Kalb et al., 2018; Islas & Ciampi, 2019; Oreja-Guevara et al., 2019). Despite marked cognitive decline affecting over 50% of diagnosed patients, limited

focus on the deficits and inadequate incorporation of routine MS-specific cognitive screenings currently exists across health settings (Foley et al., 2012; Kalb et al., 2018; Islas & Ciampi, 2019; Oreja-Guevara et al., 2019). Of note, neurological examinations serve as insufficient detectors of emerging cognitive deficits and subjective patient complaints, further necessitating the augmentation of neuropsychological testing at baseline by qualified personnel (Foley et al., 2012; Kalb et al., 2018; Islas & Ciampi, 2019; Oreja-Guevara et al., 2019). Acute neurocognitive dysfunction has been associated with intermittent relapses of the disease, in some cases resulting in permanent cognitive disability among patients who have experienced gradual decline without remission post-initial onset (Staff et al., 2009).

Identifying evidence-based, efficacious cognitive screeners to be utilized among patients with a CIS displaying symptoms suggestive of MS, or post-onset, presents as a significant obstacle due to the variety of neural compartments that may be primarily affected. Information processing has been identified as the predominant neurocognitive domain substantially impacted by CNS destruction, evoking a slower rate of processing speed that may be observed in approximately 40-70% of patients (Oreja-Guevara et al., 2019). Administration of the SDMT across settings, has demonstrated high rates of specificity, sensitivity, classification accuracy, and reliability in detecting and measuring cognitive decline in patients, particularly among those presenting with information processing deficits (Kim et al., 2017; Islas & Ciampi, 2019; Hansen et al., 2015). Further, when examined against alternate viable neuropsychological tests such as the BRB-N, the MACFIMS, the CVLT, the WMS-R, the TAP, and the BICAMS, independent utility of the SDMT faired significantly better at detecting and elucidating impairments within RRMS, SPMS, and PPMS subtypes (Kim et al., 2017; Islas & Ciampi, 2019; Hansen et al., 2015). Once deficits have been detected, non-pharmacological treatments may be initiated to inhibit rapid rates of decline, with some studies reporting cognitive improvements and emotional benefits from patient participation in cognitive training with and without neuromotor rehabilitation (Barbarulo et al., 2018; Pérez-Martín et al., 2017).

Limitations

This systematic review examined studies encompassing solely adult-onset MS cases, excluding reported research regarding the course and progression of pediatric-onsets. Data extraction was performed collectively between national and international studies. Genetic variabilities among multi-ethnic individuals, advanced or inferior availability and accessibility of medical resources, distinctions in the criteria utilized to establish a definite diagnosis, and psychometric disparities of translated neuropsychological measures resulting from the global inclusion of research may have subsequently influenced reported outcomes. In addition, a portion of the studies evaluated in this review collected data on patients diagnosed with PPMS, a rarer form of the disease, limiting generalizability to the vast majority of MS patients.

Future directions in clinical research should aim at enhancing the understanding of the detection barriers of multiple sclerosis and the clinical benefits of incorporating cognitive screenings in diagnostic workups to optimize patient outcomes. Prospective clinical studies should prolong follow-up evaluations for patients post-DMT initiation in efforts to closely monitor the long-term course of the disease across various subtypes (i.e., RRMS, SPMS).

Further advancements in the research should seek to enhance the clinical efficacy of assessing cognitive function early on for at-risk patients and those with clinically isolated syndromes (CIS), in efforts to improve the predictability of onset or provide supporting evidence to confirm its detection. Research advancements on the utility of cognitive screeners within

primary care, inpatient, and outpatient health settings to accurately detect neurocognitive decline early-on to assist in clinically managing symptoms would benefit patients experiencing functionally impairing changes and mitigate adverse effects.

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