**Introduction**

Multiple sclerosis (MS) is a chronic, demyelinating disease of the Central Nervous System known to be the most common neurological condition impacting young adults.1,2 Individuals are often diagnosed between the ages of 20 – 50 years, with women diagnosed more frequently than men (2:1). 1,2 There are three main types of MS. The majority of individuals (85% of newly diagnosed) are diagnosed with Relapsing Remitting (RRMS). 1,2 Many of these individuals progress to another type of MS, Secondary Progressive (SPMS), which is estimated to occur after roughly 10 years of the disease. 1,2 The third common type of MS is Primary Progressive (PPMS), with approximately 15% of those newly diagnosed falling into this category. 1,2 The differentiating factors between these types of MS are the occurrence (or lack of occurrence) of relapses and/or progression of disability.

MS can present with various signs and symptoms due to the variable nature of the disease and locations of lesions. There are estimated to be around 400,000 people living with MS in the United States, and potentially 200 people diagnosed each week.3 Much of literature has studied the various symptoms and conditions that develop over time for individuals diagnosed with MS. While the disease is unpredictable, common symptoms throughout the disease course may include weakness, sensation changes, fatigue, spasticity, depression, temperature sensitivities, bowel/bladder dysfunction, cognitive issues, and balance, gait, and coordination dysfunctions.1,2

The purpose of this literature review was to identify which body system(s) and function(s) demonstrate change in the early stages of MS, and if those changes are clinical or subclinical. By understanding if there are changes in those newly diagnosed with MS, health care providers, such as physical therapists, can incorporate ways to identify if changes exist in their patients, alter their treatment plan or refer if necessary, provide education, and attempt interventions that may ease or prevent future changes in these systems and/or functions.

**Literature Review**

While there are not a plethora of studies investigating changes found early in MS, there are many that present interesting results. A total of eight studies were identified and reviewed; each piece of literature contains results regarding various body system/functions. As each study assessed different topics, it is difficult to compare and contrast the methods, outcome measures, results, etc. A brief explanation of the studies, their respective results and clinical significance are discussed below, followed by the limitations that we must consider from these studies.

*Musculoskeletal-Related Changes*

Bone mineral density is the first topic of interest. Evidence has shown a potential link between Vitamin D deficiency and MS. Immobility, nutritional issues, lack of sun exposure, and other factors that may influence BMD are also often increased with long-standing disease.4 Moen et al4 investigated if individuals newly diagnosed with MS or clinically isolated syndrome (CIS) may present with decreased bone mineral density (BMD) compared to control groups. Their participants demonstrated no or little clinical disability. BMD measurements were taken for various body parts such as femoral necks, distal radius, lumbar spine, and total body. They found significantly reduced BMD (indicative of osteopenia or osteoporosis, depending on the value) for the MS and CIS groups compared to the controls for at least one site. Their results show that changes in BMD can be seen in early MS. These results are meaningful due to our ability to educate patients on the importance of physical activity to help maintain BMD measures, along with other health behaviors, such as nutrition, to promote bone health. We could also incorporate interventions that promote bone health, such as weight bearing activities.

Muscular and gait abnormalities are the next topics of interest. Gait and balance dysfunction are frequent issues with long-standing MS. Weakness, especially in the lower extremities, is also commonly found in MS. There are estimates that 50% of individuals with MS will ultimately use an assistive device within 15 years of their diagnosis.1 Kalron et al5 investigated if muscular and gait abnormalities were present for those newly diagnosed with CIS (often suspicious of MS) compared to a control group. Various measurements were taken during gait, along with measures relating to muscular strength and muscular endurance/fatigue. The CIS group showed significantly increased motor fatigue for different muscle groups and changes in various gait parameters compared to the control group. These results are meaningful as we should consider interventions that may prevent and/or delay these changes. Strengthening exercises, endurance training, and high-level mobility and gait training may prevent, delay, and/or improve these changes.

Fall and fracture risk are also important to consider. People with long-standing MS are at an increased risk for falls secondary to issues such as balance and gait dysfunction, immobility, and weakness.6 Unfortunately, considering their decreased BMD, they are also at an increased risk for fractures. Moen et al6 attempted to identify if those newly diagnosed with MS or CIS were also at an increased risk for falls and/or fractures. Of their sample, a significant number of participants from the MS and CIS groups reported falls compared to the controls. No significant differences were found between the groups for reports of fractures. These results highlight the potential importance of addressing any gait and balance dysfunctions (and other variables that may contribute to falls) that may present early in MS to try to reduce the risk of falls for these individuals. Another interesting finding in this study was the report of falls for individuals with EDSS scores of 0 and 1.0. It is important to remember even if an individual does not present with clinical disabilities, inquiring about their history of falls is still appropriate and essential in the initial evaluation. Preventive measures through interventions may also help to prevent falls and subsequent fractures for individuals who do not currently present with gait and balance dysfunctions.

*Cognitive and Emotional Changes*

Cognitive and/or emotional dysfunction are the next topics of interest. People with long-standing MS have demonstrated cognitive impairments such as decreased processing speed and memory.7 Hankomaki et al7 investigated if cognitive changes were present for those newly diagnosed with MS and also conducted a 6 year follow-up study to identify if there were changes in that time period. At baseline, cognitive deficits were found in those recently diagnosed with MS, mainly in reaction time and processing speed. At the 6 year follow-up, divided attention and processing speed were significantly worse. Consideration of these results is important for screening purposes early in the disease process to identify if a referral to a neuropsychologist, for example, is needed. Additionally, it may be necessary to adjust therapy sessions if cognitive impairments are present. For example, tasks requiring fast processing speeds may be more challenging for patients to complete. Additionally, conducting physical therapy sessions in rooms with many distractions may be more difficult for patients. Depending on the purpose of the intervention, this could or could not be a positive factor to consider. If we are trying to teach a new task, a distracting environment may make it more difficult to achieve success; a more isolated room may be more appropriate. If we know a patient has difficulty performing tasks in distracting conditions, trying to improve their performance by practicing in such an environment may be indicated.

Simioni et al8 attempted to identify cognitive deficits as well, but also desired to recognize if there are correlations with fatigue, mood disorders, and QOL for those newly diagnosed with MS. Cognitive deficits, especially in memory, attention, and executive functioning were identified. For those with cognitive impairments, an increase in anxiety, depression, and reduced QOL were also observed. This study, again, supports the idea of screening for cognitive impairments, as well as emotional dysfunction. Physical therapists should be sensitive to the psychosocial issues that the patient may be experiencing. Referrals to neuropsychologists may be indicated, even with subtle changes. Also, adapting physical therapy sessions may be necessary depending on the presentation of the individual. For example, if the patient is experiencing symptoms of depression, motivation for physical therapy may be reduced, leading to difficulty in achieving goals set in physical therapy.

Janssens et al9 conducted a study trying to identify if/what emotional changes occurred early in the disease process. These investigators found patients recently diagnosed with MS did report significantly lower QOL and higher anxiety, but found no significant difference in depression scores. The authors also identified correlations of reduced QOL and increased anxiety and depression scores for those with higher EDSS scores than those with lower EDSS scores. Again, considerations for screening and signs of emotional distress should be considered by physical therapists to refer the individual, if necessary. Additionally, as mentioned above, emotional challenges may impact one’s efforts and success with physical therapy.

*Pulmonary System Changes*

Respiratory function is the next topic of interest. Impaired respiratory function is commonly observed in neuromuscular diseases.10 These deficits often influence one’s functional exercise capacity as well. Bosnak-Guclu et al10 investigated if these changes could be observed in patients diagnosed with MS: one group diagnosed more recently and the other having a longer history of MS. The authors identified decreased pulmonary function and functional exercise capacity in both MS groups compared to the controls. Interventions to prevent, delay, and/or improve these deficits could prove to be beneficial. For example, incorporating exercises that will strengthen the respiratory muscles may improve the individual’s respiratory function. Including endurance and strengthening activities may also improve one’s functional capacity.

*Pain*

Pain is the final topic explored. Individuals with MS experience pain directly from MS, pain secondary to MS issues (e.g. spasticity), and non-MS (e.g. nonspecific low back pain). Brochet et al11 studied the prevalence, intensity, and changes in pain during the first two years after the diagnosis of MS. They did not try to identify the root cause of pain, but simply the existence of any pain. They recorded significant pain reports from those in the earlier stages of MS. Reports of pain were correlated with QOL measures. Interesting enough, the RRMS group had improved QOL measure scores whereas the PPMS group did not. Considerations from this study include the need to screen for pain, identifying what the root source may be (MS, secondary to MS, non-MS) and address the pain accordingly. Physical therapy is clearly indicated for non-MS and may also help to decrease pain secondary to MS, such as pain from increased spasticity by helping to achieve better alignment, learning to perform activities and positions that may not influence spasticity, manual therapy, and other therapeutic activities.

*Limitations*

All of these observational studies have identified potential changes to various body systems and functions, with and without the presentation of clinical disabilities. Interestingly, there were many common limitations in these studies that should be acknowledged. First, many of these studies consisted of small sample sizes. These studies selected individuals from specific areas, some even from the same hospital, as opposed to a more random selection of patients with MS. None of the authors explained why they selected the number of participants for their studies. Perhaps there would have been other significant findings had they identified an appropriate sample size. Additionally, some studies did not explain their recruiting and selection process. If the authors are at will to select whomever (selection bias), we may have a misrepresentation of a population with MS demonstrating certain characteristics.

Second, there was a lack of acknowledging whether the assessors were blinded to the various MS or CIS and control groups in some of the studies. While studies that incorporated questionnaires with specific questions may not be biased, assessments, such as clinical testing for pulmonary index, may be influenced if the assessor is aware of the participant’s group.

Third, there are variable definitions for newly diagnosed between the studies. Even by trying to identify a more “homogeneous” group of participants by narrowing down to newly diagnosed, some patients who are newly diagnosed may or may not present with clinical disabilities, and may have been diagnosed more or less recently after their first symptom than others. Some studies acknowledged the variation in disabilities by either accepting certain EDSS levels, or by dividing their study into two groups (one with lower and one with higher EDSS scores). The range of EDSS scores were 0-6 for all participants across these eight studies. Many of the studies did present with an average EDSS score of 2.0 or less. Is this representative of the common clinical presentation of individuals newly diagnosed with MS? As discussed before, MS is extremely variable, so we should not simply assume patients newly diagnosed with MS will present similarly. It is known that a diagnosis of MS may take time, and some receive their diagnosis many years after their first symptoms. As a result, some may already have progressed to SPMS. Also, those diagnosed with PPMS may present with much higher EDSS scores. We must also acknowledge that an individual diagnosed at a younger age may present with different findings based on age-related changes. The average age for all of these studies were between 32 and 39 years of age with various standard deviations (most less than 10 years of age). Would a 20 year old present with similar decreases in BMD compared to a 40 year old? These are just examples of questions to consider when reviewing the literature.

Fourth, there is a potential difficulty in performing and identifying these changes with a screening tool. While the discussion of clinical implications is to attempt to screen individuals for these changes, this may be difficult to perform. For example, it may be challenging to note gait changes without a GAITRite system that can provide measurements of the gait variables. Another example, we are not able to perform a bone scan, so identifying if an individual presents with decreased BMD is not realistic. Therefore, it’s important to understand that these changes could be present, and incorporate this knowledge into practice. This may range from simply educating the patient that such changes may exist, to providing interventions that theoretically could prevent or delay such changes. If the patient has been screened, and issues have been identified, such as decreased BMD, cognitive changes, etc, we can acknowledge these changes and try to incorporate interventions that we theoretically believe could help to maintain or improve such issues.

A fifth and final limitation to consider from these studies is the lack in identifying more important background information. For example, the amount of, or lack of, physical activity could significantly influence BMD scores, emotional well-being, pulmonary function, functional capacity, etc. None of these studies recognized such an influential factor. Studies have shown the benefits of physical activity on fatigue, QOL, and other areas. Many symptoms of MS are interconnected, and therefore can be influenced by even just one variable. For example, if someone is physically active and experiences less fatigue than someone who does not participate in activities, there may be a difference in reports of depression and QOL measures. Undoubtedly it is challenging to identify every variable that could influence the various outcome measures utilized in these studies. While these authors did not consider the participant’s current level, or history, of physical activity, perhaps future research will acknowledge and study its influence upon the various systems and functions.

**Further Considerations**

These introductory studies have successfully identified various system/functional changes in early MS for individuals that present with little or no clinical disabilities. As discussed earlier, a main takeaway from these studies is the importance of screening for symptoms early in MS. Screening may help to identify if a referral to another specialist is necessary, and may also identify other areas that we can target through physical therapy sessions. However, it may be challenging to screen for these changes. While significant differences were found statistically, how obvious might these changes be to us clinically? If changes are not observed via clinical screens, then understanding that subtle changes may exist could help to provide interventions to try to prevent or delay the potential increase in these changes with disease progression. Perhaps further studies can attempt to identify appropriate screening tools to be used in the clinic to help identify these subtle changes.

The lack of literature related to early changes in MS should also be addressed. While the eight articles discussed in this paper have identified changes, better quality and larger size studies may help to confirm or disprove some of the changes noted. It may help if investigators utilize common clinical screening tools, in addition to the more specific laboratory tools that may not be realistic in the clinic, to better advise therapists and other healthcare practitioners of what may be expected clinically. Additionally, these studies should spark interest and need in identifying interventions that can help prevent, delay, and/or improve any of the changes noted early in MS. Interventions may include physical therapy, cognitive therapy, nutritional supplements, etc.

**Conclusions**

Many investigators have identified changes in body systems and functions for those recently diagnosed with MS. While all of these studies are not necessarily comprised of the highest quality evidence, their results may have clinical implications for physical therapists. Screening and providing interventions upon the theoretical basis that these changes may exist could lead to clinical decisions for interventions at this time. Further research confirming these changes as well as identifying evidence-based interventions that may successfully prevent, delay, and/or reduce these changes are indicated at this time.

This literature review provides information for part of a capstone project that consists of a wellness event for those newly diagnosed with MS. With this information, we can provide patient education regarding these potential changes and the theoretical actions that may help to prevent, delay, or address these changes. The wellness event is meant to educate and empower individuals who are newly diagnosed with MS to have more positive outcome expectations and improved self-efficacy to either initiate or maintain healthy behaviors. One aspect of the wellness event is to provide a one on one screening/evaluation for participants to provide an individualized wellness plan. Incorporating the results from this literature review may assist us in providing an improved, comprehensive individualized wellness program by ensuring we address some of these changes that may be found for those who are recently diagnosed with MS.

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