Physical Activity in Pediatric Multiple Sclerosis—Can Lifestyle Factors Affect Disease Outcomes?

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Abstract

Currently, little to no information is available about interventions that can ameliorate symptoms such as depression and fatigue in children and adolescents with multiple sclerosis (MS), nor is there clear information on modifiable factors that can provide neuroprotection in this population. However, physical activity (PA) may have significant effects on disease activity, future disability, cognition, and symptoms of depression and fatigue in pediatric MS. The extent of this effect is unknown. In this paper, after providing an overview of definitions of and outcomes in pediatric MS, we provide a review of existing literature relating PA to outcomes in MS, and then turn to a review of the complex relationship between PA, neuroinflammation, and outcomes in the pediatric population.

Keywords

Pediatric, multiple sclerosis, physical activity, outcome, fatigue, depression, exercise, review

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Demyelinating disorders of the central nervous system (CNS) occur in approximately 1/100,000 children. About one-fifth of these children will eventually receive a diagnosis of multiple sclerosis (MS).[1] These cases constitute approximately 2–5 % of all cases of MS.[2] Of these children, up to three-quarters will experience cognitive decline, depression, and/or fatigue, and irreversible motor disability occurs at a young age, on average 2 decades after disease onset, or in the fourth decade of life. Currently, little to no information is available about interventions that can ameliorate symptoms such as depression and fatigue in children and adolescents with MS. Cross-sectional studies in healthy adolescents have suggested relationships between higher levels of physical activity (PA) and cognitive outcomes, brain volumes, psychosocial outcomes, and academic achievement. Adult MS studies have shown PA to benefit cognition and psychosocial outcomes. Improvement in levels of PA in this population may provide a simple, nonpharmacologic means by which to reach this goal. In this paper, after providing background information on pediatric demyelinating disorders, we will move on to an overview of studies focused on the relationship between physical activity, neuroinflammation, and outcomes in MS and in the pediatric population.

Background—Pediatric Demyelinating Disorders

Definitions

Pediatric demyelinating disorders can be divided broadly into recurrent and monophasic entities, including acute disseminated encephalomyelitis (ADEM), clinically isolated syndrome (CIS), and MS, in addition to entities such as neuromyelitis optica and recurrent optic neuritis/chronic relapsing inflammatory optic neuropathy. Currently, magnetic resonance imaging (MRI) and clinical parameters fulfilling criteria for dissemination in space and time appear to be suitable for diagnosing MS in childhood. While the 2005 McDonald criteria were found to have poor specificity and sensitivity for pediatric MS,[3,4] the revised McDonald MRI Criteria[5] are sensitive and specific for the diagnosis of MS in children >11 years of age.[6] In brief, in children over 11 years of age, demonstration of dissemination in time can be accomplished by using a single MRI timepoint with evidence for enhancing and nonenhancing lesions in areas typical for MS, whereas dissemination in space can be demonstrated by greater or equal to one lesion in at least two of the four following regions: periventricular, juxtacortical, infratentorial, spinal cord. Younger children who present with multifocal demyelination diagnosed as ADEM should have two or more non-ADEM attacks or one ADEM attack followed by a nonencephalopathic clinical attack and accrual of lesions satisfying McDonald Criteria.[5,7]

Increased Disease Burden in Children with Multiple Sclerosis

Pediatric onset MS is characterized by greater MRI disease burden both early on in the disease and at later stages,[8,9] with evidence for accelerated disease burden in comparison with the adult population. Children with MS have a higher T1 lesion volume on brain MRI, a higher

T1 lesion volume to brain parenchymal volume ratio, and a lower magnetization transfer in T2 lesions as well as in normal appearing gray matter (GM) and white matter compared with adults with similar disease duration. Patients with longstanding pediatric-onset disease compared with those with longstanding adult onset disease of similar duration have no significant differences in quantitative measures including GM fraction, white matter fraction, T1 lesion volume, T2 lesion volume, and brain parenchymal fraction.[9] As a brain volume loss of 0.2 % per year between the ages of 30–50 is anticipated as part of the normal aging process,[10] the presence of similar brain parenchymal fraction in these two groups suggests more aggressive disease in pediatric-onset compared with adult-onset MS. This has been further supported by studies reporting decreased head size in children with MS.[11]

As in adult MS, GM atrophy can occur early in the course of pediatric onset MS.[9,12] GM atrophy in the thalamus has been described in pediatric onset MS after a mean disease duration of 3 years. However, unlike the adult population, where correlations between GM atrophy and disability have been found,[10] there appears to be no correlation between GM volume loss and disease duration or physical disability in pediatric onset MS with relatively short disease duration.[9,12] Importantly, while at onset GM involvement in pediatric populations may be limited,[13,14] the rate of progression of GM atrophy is similar between adult onset and pediatric onset relapsing-remitting-MS (RR-MS) patients.[14] This is corroborated by findings in a long-term follow-up study, in which no differences were seen in regional GM atrophy between age- and disease-duration-matched adult- and pediatric-onset MS patients.[15] Thus, multiple MRI studies have demonstrated clear evidence for high disease activity and progressive atrophy in individuals with pediatric onset MS.

Finally, clinical relapses in pediatric MS are reported to be more frequent than in the adult population, occurring at a rate of 1.13 relapses per year compared with 0.4 relapses per year in the adult population.[16] Indeed, a first interattack interval of less than a year is reported in 60 % of patients with pediatric MS.[16] An interattack interval of less than a year in addition to high relapse frequency in the first 2 years after diagnosis is predictive of secondary progression and earlier progression to irreversible disability in pediatric patients.[17]

Psychosocial and Physical Burden of Pediatric Multiple Sclerosis

Despite evidence for greater disease severity in pediatric MS, natural history studies have suggested a relatively slow accrual of physical disability in this population. On average, the patient with pediatric onset MS will reach a point of irreversible disability (Expanded Disability Severity Scale [EDSS] ≥4) approximately 20 years after disease onset compared with 10 years in adult-onset patients.[18] Nonetheless, the burden of non-motor disability is high as the majority of children and adolescents with MS may suffer from depression, fatigue, or cognitive impairment.[19,20]

Cognitive impairment may occur early on in the disease course, with one study suggesting a deterioration on neurocognitive testing in 75 % of pediatric onset patients within 2 years of disease onset.[21] At 5 years, a small number of children in the same cohort were noted to have improvements in performance (25 %), with over half (56 %) of these patients experiencing deterioration from onset.[22]

Depression is seen in almost one-third of children with acquired demyelinating syndromes, with fatigue in one-quarter.[19,23] No large-scale studies evaluating longer-term occupational and social outcomes of this population have been published, but one small cohort of MS patients (n=19) with pediatric onset disease suggests a downward educational trajectory, as represented by greater need for school supports and worsening academic performance.[24]

Currently, little to no information is available about interventions that can ameliorate symptoms, such as depression and fatigue in children and adolescents with MS, nor is there clear information on modifiable factors that can provide neuroprotection in this population. However, growing literature supports an association between higher levels of PA and improved outcomes in both pediatric populations and adults with MS. The remainder of this review paper will be devoted to a brief consideration of the literature on PA in MS and pediatric populations.

Physical Activity in Pediatric Populations—Effect on Inflammation, Fatigue, Depression, and Cognition

Researchers have examined relationships between PA and neurocognitive and psychosocial outcomes in both healthy children and children with chronic illnesses such as chronic fatigue syndrome, pediatric cancer (acute lymphoblastic leukemia [ALL]), pediatric lupus, and juvenile idiopathic arthritis (JIA). This work has suggested that exercise interventions may lead to improvements in well-being, fatigue, and depression, as has adult literature focusing on MS[25–30] and chronic illnesses.[31] For example, in JIA, an 8-week dedicated program of aerobic training has led to increases in aerobic capacity, as well as improvements in a health index (childhood health assessment questionnaire, [CHAQ] [0.77 ± 0.61 to 0.20 ± 0.28; $p<0.001$]).[32] However, another study has suggested that improvements in well being (CHAQ) after an exercise intervention may be small.[33] In terms of depression in children, several studies have suggested improvements in self-reported measures of depression and self-worth in obese children, including a randomized controlled trial (RCT) comparing usual care to an exercise intervention (n=81),[34] and another RCT comparing two different prescribed exercise lengths (0 versus 20 minutes versus 40 minutes, n=207).[35]

Much research on the effects of exercise as an intervention for cancer-related fatigue in adults has been published, showing moderate effects on sleep, depression, and fatigue.[36] Studies in the pediatric cancer population have indicated low levels of fitness and high levels of fatigue, but only one study has assessed the specific effects of exercise on well-being, fatigue, and depression in this population, and did not report significant effects.[37]

As for effects on cognition, multicomponent interventions focusing on increasing PA have resulted in improvements in cognition, mathematics, and reading scores in healthy children,[38,39] while effects on executive function[40] have been reported in a randomized exercise trial in an obese pediatric population. Furthermore, healthy children (n=221) exhibited both increased fitness and improvements in cognitive flexibility (4.8 %, 95 % confidence interval [CI] 1.1 to 8.4; d=0.35 for group difference in pre-to-post change score) and inhibition (3.2 %, 95 % CI 0.0 to 6.5; d=0.27) after undergoing a school-based PA intervention.[41] Structural and functional changes, namely changes in hippocampal size and memory, have been found in older adults after an exercise intervention,[42] while in healthy adolescents, children with greater fitness levels have been found to have greater volumes in the deep GM.[43]

Finally, PA and fitness may mediate inflammation in children. While exercise may acutely increase systemic inflammation in the pediatric

population,[44] it has been found to be well tolerated in children with chronic inflammatory conditions, such as JIA and systemic lupus erythematosis (SLE).[25] Moreover, the long-term effects of exercise and increased fitness may be anti-inflammatory: one study of a 9-month fitness-based curriculum in non-obese middle school students demonstrated both increased fitness and lowered tumor necrosis factor (TNF)-alpha levels (–2.55 ± 1.79 pg/ml; p<0.001).[45]

Physical Activity in Adult Multiple Sclerosis

Studies from North America have documented lower rates of PA in people with MS than healthy controls via survey data[46,47] and using objective measures (accelerometry data: d=0.68, F=47.2; p<0.001).[48] Furthermore, a meta-analysis of studies of PA in MS has reported that PA levels in the adult MS population are 1 standard deviation (SD) below that of healthy controls.[49]

Higher levels of PA may have effects on disease activity and common symptoms associated with MS. For example, in the adult MS population, level of premorbid PA predicts worsening of disability scores over 2-year follow-up.[50] One large survey suggests associations between increased PA and both overall health-related quality of life (HRQOL) and HRQOL subscales (physical health, improvements in health, energy subscale, social function subscale) as well as decreased relapse rate (p=0.009).[51] The relationship between HRQOL and PA is complex, and the relationship may be indirect. In another study of 292 MS patients that evaluated QOL, disability, PA (self-reported and accelerometer), mood, pain, self-efficacy and self-report, lower levels of fatigue, depression, anxiety and pain, and higher levels of social support and MS self-efficacy had higher levels of QOL.[52]

In adult MS, aerobic training has improved fatigue, depression, and anger scores over the course of 10 to 12 weeks.[30,53] Another study evaluating the effects of two exercise training programs in MS over the course of 2 months (patients n=30; controls n=15) suggests that both patients undergoing resistance training and those undergoing lower limb strengthening and balancing exercises benefitted in several areas whereas controls showed no improvement.[54] In addition, patients undergoing either form of exercise training were found to have improvements in fatigue and depression.

These benefits may last beyond the intervention period: one study found that improvements in QOL and fatigue persisted 3 months after discontinuation of the program.[30] Shorter-term programs may have benefits: one 4-week program showed an improvement in aerobic capacity in addition to an improvement of health perception and a tendency to less fatigue. Symptom exacerbation was low (6 %).[55]

It is possible that PA in any form may be beneficial in the MS population. A longer-term study evaluating yoga and exercise has suggested benefits of a 6-month yoga or exercise class on fatigue compared with a control condition.[56] This is supported by recent studies focusing on sedentary behavior in MS[57] and active commuting in healthy pediatric and adult populations,[58,59] suggesting a beneficial effect related to overall increase in PA regardless of level of aerobic activity. The relationship between frequent symptoms such as fatigue and physical activity, however, is complex, as one study has suggested only a weak relationship between fatigue and PA, while age, type of MS, anxiety, and depression mitigated this relationship.[60]

Physical Activity in Pediatric Multiple Sclerosis

Information regarding exercise and PA in pediatric MS is lacking, but some data suggesting conditions associated with decreased PA may have an effect on MS in children. Obesity has been identified as a major problem in pediatric onset MS, with an odds ratio for receiving the diagnosis of MS/CIS of 3.76 (1.54–9.16) in extremely obese (BMI ≥35 kg/m^2) girls in California.[61] In other work, obesity at age 18 was associated with a twofold increased risk for MS in two large cohorts of women (Nurses' Health Study).[62] Indirect support for the role of exercise, physical activity, and fitness on systemic inflammation can be seen in research demonstrating an elevation of inflammatory markers in non-obese children with higher body fat and lower fitness levels.[63]

Our preliminary data evaluating levels of PA in pediatric MS compared with children with monophasic demyelinating disorders suggests significantly lower participation in strenuous activities in the MS population (n=23) in comparison to children with monophasic demyelination (n=52) (70 % versus 90 %; p=0.03).[64] In our study, moderate PA had no correlation with depression and fatigue, but strenuous PA significantly correlated with lower levels of general fatigue (r=–0.45), suggesting a possible relationship between common symptoms associated with MS and higher-intensity PA. Children with longer disease duration were less likely to participate in strenuous PA (r=–0.51). We have demonstrated correlations between low levels of PA self-efficacy and mild PA, and high levels of PA self-efficacy and participation in strenuous PA, suggesting a relationship between higher rates of PA self-efficacy and greater engagement in strenuous types of PA in this population.[65]

While the associations between PA and psychosocial outcomes in pediatric MS have not been investigated, research in healthy Canadian children demonstrating associations between PA and increased risk for obesity and poor HRQOL[66] suggests the need for close examination of this matter in children with MS.

Conclusions

Pediatric MS carries with it a high disease burden and poor cognitive and psychosocial outcomes. Development of interventions focused on preventing, slowing, and remediating these outcomes is imperative. We believe that participation in PA holds considerable promise as a behavior intervention. Our preliminary cross-sectional work suggests that children with MS engage in less PA than children who have recovered from a monophasic demyelinating attack. Further, there is a strong basis for PA as a behavioral intervention based on research reviewed for adolescent populations with and without disease, and in adults with MS. Further studies should examine the potential neuroprotective effects of PA and establish the level of PA and fitness that may be effective for an interventional program. If, indeed, higher levels of general PA can help to ameliorate MS-related symptoms and, potentially, affect disease progression, flexible, home-/distance-based interventions that would be feasible for this population could be crafted. Such strategies would have the potential to translate to other flexible, potentially technology-based patient-centered interventions, including those focused on medication adherence and symptom management. This is an important next step in research involving pediatric MS. ■

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