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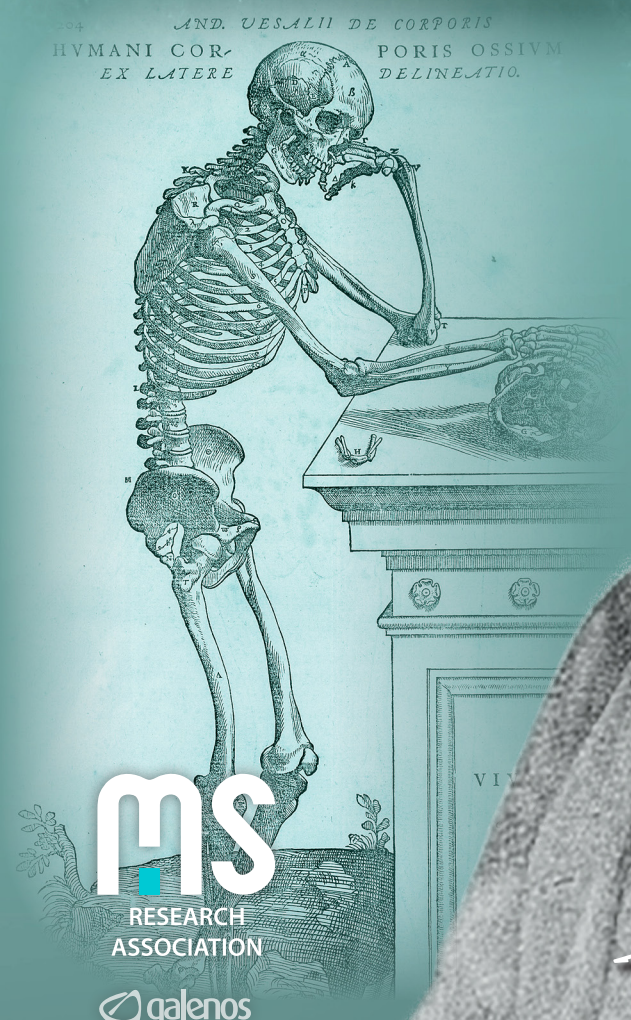

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Journal of
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Journal of MULTIPLE SCLEROSIS Research

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Preparation of Manuscript

Manuscripts should be prepared according to ICMJE guidelines (http://www.icmje.org).

Original manuscripts require a structured abstract. Each section of the structured abstract must be labelled with the appropriate subheading (Objective, Materials and Methods, Results, and Conclusion). Case reports require short unstructured abstracts, whereas letters to the editor do not require an abstract. Research or project support should be acknowledged as a footnote on the title page.

Technical and other assistance should be provided on the title page.

Preparation of research articles, systematic reviews, and meta-analyses must comply with study design guidelines:

CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001;285:1987-1991) (http://www.consort-statement.org/);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009;6(7):e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Toward complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-44.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

Meta-analysis of observational Studies in Epidemiology (MOOSE) guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting MOOSE group. JAMA 2000;283:2008-2012).

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Writing rules

The submission should be split into separate files in the following order:

a. Title

b. Main Document (English abstract and keywords-Turkish abstract and keywords, main text, references, tables and figure explanations should be included).

c. Figures, pictures and graphics files in .jpeg or .gif formats should be uploaded separately.

d. Copyright Transfer Form and Authorship Contribution Form

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Title: The title should provide important information regarding the manuscript's content. The title page should include the authors' names, degrees, and institutional/professional affiliations, a short title, abbreviations, keywords, financial disclosure statement, and conflict of interest statement. If a manuscript includes authors from more than one institution, each author's name should be followed by a superscript number corresponding to their institution, which is listed separately. The contact information for the corresponding author should also be provided, including name, e-mail address, telephone, and fax numbers.

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Abstract and Keywords: The second page should include an abstract not exceeding 250 words. Moreover, as various electronic databases integrate only abstracts into their index, important findings should be presented in the abstract.

Abstract

The abstract should be short and factual. It should state the purpose of the research briefly and should be structured according to the following subheadings: Objective, Materials and Methods, Results, and Conclusion. Abbreviations should be avoided and reference citations are not permitted. References should be avoided, and nonstandard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself. The clinical trial number should be provided at the end of the abstract.

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Materials and Methods: Important methods should be written respectively.

Results: Important findings and results should be provided here.

Conclusion: The study's new and important findings should be highlighted and interpreted.

Other types of manuscripts, such as case reports, reviews, and others, will be published according to uniform requirements.

Keywords: Provide at least three keywords below the abstract to assist indexers. Use terms from the Index Medicus Medical Subject Headings List (for randomized studies, a CONSORT abstract should be provided (http://www.consort-statement.org).

1. Original Articles:

An article is considered original research if;

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- The researchers describe their hypothesis or research question and the purpose of the study.
- The researchers detail their research methods.
- The results of the research are reported.
- The researchers interpret their results and discuss possible implications.

This is the most common type of journal manuscript used to publish full data reports from research. It may be called an Original Article, Research Article, Research, or just Article, depending on the journal.

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Original articles should have the following sections:

Introduction: The introduction should include an overview of the relevant literature presented in summary form (one page), and whatever remains interesting, unique, problematic, relevant, or unknown about the topic must be specified. The introduction should conclude with the rationale for the study and its design and objective(s).

Materials and Methods: The selection of observational or experimental participants, such as patients, laboratory animals, and controls, must be clearly described, including inclusion and exclusion criteria and a description of the source population. Sufficiently detailed methods and procedures must be identified to allow other researchers to reproduce the results. References to established methods (including statistical methods) and to brief modified methods and the rationale for using them and evaluation of their limitations must be provided. All drugs and chemicals used, including generic names, doses, and routes of administration, must be identified. The section should include only information that was available at the time the plan or protocol for the study was devised on STROBE (http://www.strobe-statement.org).

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Discussion: This section should include a discussion of the data. New and important findings/results and the conclusions they lead to should be emphasized. The conclusions should be linked with the goals of the study, but unqualified statements and conclusions not entirely supported by the data should be avoided. The detailed findings/results should not be repeated; important findings/results should be compared with those of similar studies in the literature, along with a summary. In other words, similarities or differences in the obtained findings/results with those previously reported should be discussed.

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Conclusion: The conclusion of the study should be highlighted.

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> **Abstract:** an unstructured abstract that summarizes the case
>
> **Introduction:** a brief introduction (recommended length: 1–2 paragraphs)
>
> **Case Presentation:** describes the case in detail, including the initial diagnosis and outcome
>
> **Discussion:** should include a brief review of the relevant literature and how the presented case furthers our understanding to the disease process

3. Review Articles: Review articles provide a comprehensive summary of research on a certain topic and a perspective on the state of the field and where it is heading. They are often written by leaders in a particular discipline after an invitation from the editors of a journal.

Review articles should include a conclusion in which a new hypothesis or study about the subject may be posited. Methods for literature search or level of evidence should not be published. Authors who will prepare review articles should already have published research articles on the relevant subject. There should be a maximum of two authors for review articles.

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https://www.nlm.nih.gov/bsd/uniform_requirements.html

Examples of References

1. List All Authors

Bonanni E, Tognoni G, Maestri M, Salvati N, Fabbrini M, Borghetti D, DiCoscio E, Choub A, Sposito R, Pagni C, Iudice A, Murri L.

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Sleep disturbancesin elderly subjects: an epidemiological survey in an Italian district. ActaNeurol Scand 2010;122:389-397.

2. Organization as Author

American Geriatrics Society 2015 Updated Beers Criteria Expert panel. American geriatrics society 2015 updated Beer criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2015;63: 2227-2246.

3. Complete Book

Ham RJ, Sloane PD, Warshaw GA, Potter JF, Flaherty E. Ham's primary care geriatrics : a case-based approach, 6th ed. Philadelphia, Elsevier/Saunders, 2014.

4. Chapter in Book

BG Katzung. Special Aspects of Geriatric Pharmacology, In:Bertram G. Katzung,Susan B. Masters, Anthony J. Trevor (Eds). Basic and Clinical Pharmacology. 10th edition, Lange, Mc Graw Hill, USA 2007, pp 983-90.

5. Abstract

Reichenbach S, Dieppe P, Nuesch E, Williams S, Villiger PM, Juni P. Association of bone attrition with knee pain, stiffness and disability; a cross sectional study. Ann Rheum Dis 2011;70:293-8. (abstract).

6. Letter to the Editor

Rovner B. The Role of the Annals of Geriatric Medicine and Research as a Platform for Validating Smart Healthcare Devices for Older Adults. Ann Geriatr. 2017;21:215-216.

7. Supplement

Garfinkel D. The tsunami in 21st century healthcare: The age-related vicious circle of co-morbidity - multiple symptoms - over-diagnosis - over treatment - polypharmacy [abstract]. J Nutr Health Aging 2013;17(Suppl 1):224-227.

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Tables: Each table should be supplied on a separate file. Tables should be numbered according to the order in which they appear in the text, and a brief caption for each should be supplied. Each column must have a short or abbreviated heading. Explanatory statistical measures of variation, such as standard deviation or standard error of the mean, must be written. Each table must be cited in the text.

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Type of Article	Abstract	Word Count*	Number of References	Tables/ Figures
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Review Articles	250	3500	100	5
Invited Review Article	250	3500	75	5
Case Reports	100	1000	15	2
Images	None	500	10	2
Letters to the Editor	None	600	10	1
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All authors are responsible for the manuscript's content.

All authors participated in the study concept and design, analysis and interpretation of the data, and drafting or revising of the manuscript and have approved the manuscript as submitted.

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PEER REVIEW

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Approval of the Ethics Committee and a statement on the adherence of the study protocol to international guidelines (Declaration of Helsinki revised in 2013 [www.wma.net/e/policy/b3.html]) are required for experimental and clinical studies as well as studies on drug–human interactions. In experimental animal studies, the authors should indicate that the procedures were followed in accordance with animal rights (Guide for the Care and Use of Laboratory Animals [https://www.nap.edu/catalog/5140/]) and should obtain approval from the Animal Ethics Committee.

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Journal of Multiple Sclerosis Research 2023;3(3):40-45

RESEARCH ARTICLE

Assessing Psychiatric Symptoms in Pediatric Multiple Sclerosis Patients

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Abstract

Objective: Multiple sclerosis (MS) is an autoimmune disease affecting both adults and children, often accompanied by various psychiatric disorders. Research on psychiatric symptoms in pediatric MS is relatively limited in comparison with adult-onset MS. To evaluate depression and anxiety levels in pediatric MS patients and compare them to healthy controls, and to assess the impact of clinical and sociodemographic variables on these levels.

Materials and Methods: A cross-sectional study was conducted involving 15 pediatric MS patients and 15 age and socioeconomic-matched healthy controls. Anxiety and depression levels were assessed using the State-Trait Anxiety Inventory (STAI) and Children's Depression Inventory (CDI).

Results: No significant difference was observed between the MS group and controls in terms of CDI scores, STAI state, and anxiety trait scores. Nevertheless, individuals in the MS group exhibited higher levels of trait anxiety. The average disability score among MS participants was low (0.33), potentially explaining the comparable psychiatric symptom levels with the controls. Sociodemographic data revealed a significant difference in fathers' education levels between the groups.

Conclusion: Depression and anxiety levels in pediatric MS patients were similar to healthy controls, possibly attributed to the low disability levels in the MS group. Extensive research is crucial to understand better psychiatric comorbidities and their correlation with disability progression in pediatric MS.

Keywords: Multiple sclerosis, pediatric, psychiatric symptoms

Introduction

Multiple Sclerosis (MS) is an autoimmune and chronic disorder that incites inflammatory damage to the myelin sheath, and while it is more prevalent among young adults, children can also be affected by MS. It is reported that between 3% and 10% of MS patients are under 16, and less than 1% of MS occurs in children younger than 10 (1). Pediatric MS patients tend to experience a broader range of symptoms at the onset of the disease, but despite the symptom variety, pediatric MS patients have a lower likelihood of developing progressive disease compared to adult MS patients (2,3). Timely diagnosis and effective management of MS in pediatric patients are critical as individuals in this age group tend to experience significant disabilities at an earlier stage of life than adults, and taking disease-modifying drugs at an early stage may help slow down the disease's progression (4,5). Although early diagnosis is critical, pediatric MS can be difficult to differentiate from other various diseases in children, leading to an underdiagnosis or a misdiagnosis (6,7). Recently, there has been a surge in research related to pediatric MS, which has led to a greater understanding of the condition and a continued interest in this field.

Extensive studies have investigated the correlation between neurological and psychiatric disorders. It has been particularly

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demonstrated by different studies that anxiety disorders and depression frequently accompany adult MS (8,9). Depression, in particular, is one of the most important problems associated with MS, and MS-related depression is generally reported to be of moderate severity (10). In different studies, depression has been shown to affect approximately 15.8% to 47% of the MS population (11-13). The lifetime prevalence of comorbid depression in MS patients is estimated at around 50% (14,15). Anxiety concerns approximately 16-48% of individuals with MS, and patients with low or moderate disabilities reportedly exhibit higher anxiety levels (16-19). This phenomenon has been explained by the fact that patients fear more severe disabilities in the future due to the knowledge of how debilitating their moderate handicaps can be. Fatigue and pain, which are frequently seen in MS, are also found to be associated with anxiety and depression (19).

Accurate recognition of psychiatric disorders accompanying MS and making the necessary interventions are essential in many different aspects. MS patients often experience secondary consequences due to depressive symptoms, including various physical and psychological effects (20). For instance, individuals with MS who experience depression are at an increased risk of premature mortality and suicide (21). Depression exerts a significant negative impact on the quality of life, level of independence in daily activities, and employment status of individuals with MS (22,23). Research has further suggested that depression may play a role in worsening fatigue and pain symptoms in individuals with MS (24,25). Depression among individuals with MS has also been found to exhibit a correlation with reduced adherence to medications, heightened disease severity, and deteriorating disability (26-28). Similarly, investigating the presence of anxiety is crucial for MS patients as, if remains untreated it can remarkably affect the quality of life, treatment adherence, and symptoms (29).

Depression and anxiety are linked with MS in adults, and studies suggest similar issues in pediatric MS. There is a great body of literature on psychiatric disorders accompanying adult-onset MS, whereas there are fewer studies on psychiatric disorders concomitant with pediatric MS. A limited number of studies reported that depression is present in 50% of children and adolescents with MS (30,31). In another study conducted with pediatric MS patients, anxiety disorder was found to be the most common psychiatric disorder among the sample (32). While data on the neurological attributes of pediatric MS is gradually accumulating, information about the psychiatric features of these children remains scarce. In order to enhance the quality of life and promote treatment adherence for pediatric patients with MS, it is imperative to gain a deeper understanding of the psychiatric comorbidities that often accompany this condition. Such knowledge can aid in the development of effective intervention strategies aimed at improving outcomes for this vulnerable population.

This study seeks to assess the levels of depression and anxiety in pediatric MS patients and draw a comparison with healthy controls. Furthermore, the objective of our investigation was to evaluate the potential impact of clinical and sociodemographic variables on the levels of depression and anxiety observed in children diagnosed with MS. The main hypothesis of our research was that depression and anxiety levels would be higher in children with MS than in healthy controls.

Materials and Methods

Fifteen children and adolescents with a MS diagnosis and 15 healthy controls matched with them in terms of age and socioeconomic level were included in our study after obtaining ethical approval from the ethics committee. Healthy controls were recruited for the study by placing an announcement in the hospital. Prior to the study, we obtained informed consent from all participants and their parents. The ethical committee approval number for our study is 2023/265. The diagnosis of children with MS evaluated within the scope of our study were made using the 2017 McDonald Criteria which have been shown to be equally applicable for pediatric onset MS (33). The inclusion criteria for children with MS were to be regularly followed up at the neurology clinic of Kocaeli University Faculty of Medicine with a definitive MS diagnosis. There was no specified age range among the inclusion criteria for the study and all eligible patients under 18 years of age were included. There were no specific exclusion criteria for the MS group except for failing to complete the necessary forms or withholding consent. In addition to the exclusion criteria valid for the MS group, having a neurological or other chronic medical disease was an exclusion criterion for the control group. The sociodemographic information of the participants was obtained through a sociodemographic form filled out by the researchers who conducted the interview. Depressive symptom levels of the participants were evaluated using the Children's Depression Inventory (CDI), and their anxiety levels were assessed using The State-Trait Anxiety Inventory (STAI).

The Children's Depression Inventory: Depression levels were measured by the CDI, a self-report scale assessing depression in children and adolescents. The scale comprises 27 Likert-type items rated on a scale of 0 to 2. The total score on the scale ranges from 0 to 54, with higher scores indicating greater severity of depression. To identify clinical depression, a score higher than 19 is considered the criterion (34,35).

The State-Trait Anxiety Inventory: The STAI assessment tool comprises two scales, each consisting of 20 items. Items 1-20 measure state anxiety (STAI-S), and 21-40 measure trait anxiety (STAI-T) (36). Each form allows for a minimum score of 20 and a maximum of 80, with each item scored from one to four (37).

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23.0. The Shapiro-Wilk test was utilized to define the normality of data distribution. Continous variables (e.g., age, CDI and STAI-C scores) were analyzed using the Mann-Whitney U test. Chi-squared and Fisher's exact tests were utilized for the categorical variables. The associations between scale scores and continuous sociodemographic data were examined with the Spearman's correlation test. All statistical tests conducted had a significance threshold of 0.05 and were two-tailed.

Results

A comparison of the sociodemographic data of the cases is presented in Table 1.

When the patients in the MS group were evaluated, the average age of diagnosis was found to be 12.90 (±3.05). The average duration of the disease was found to be 2.46 (±1.68) and the average number of attacks was 1.53 (±0.63). When average disability score (EDSS) scores were examined, the average score was found to be 0.33 (±0.72). The treatment agents of adolescents with MS are shown in Figure 1.

When the two groups were compared regarding CDI scores, STAI state, and anxiety trait scores, no significant difference was found between the groups. However, it was observed that the trait anxiety levels of adolescents with MS were higher than those of the control group. The comparison of scale scores across the groups is presented in Table 2.

In the MS group, no significant association was found between the scale scores and disease duration, number of attacks, age at diagnosis, and EDSS scores (all for p>0.05).

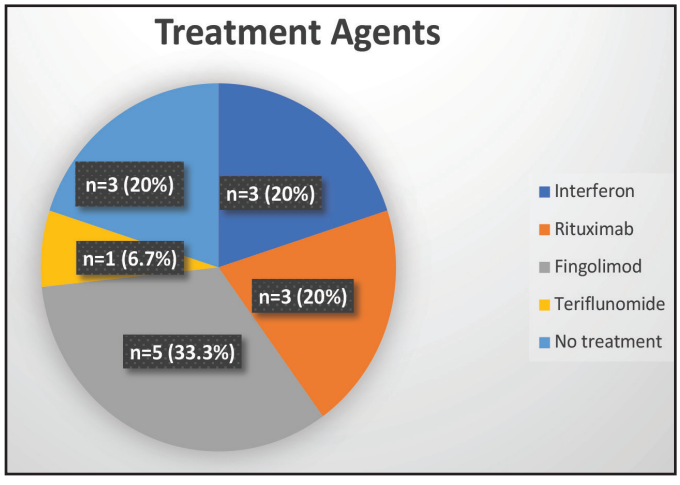

Figure 1. Treatment agents used in multiple sclerosis group

Discussion

This study aimed to examine the anxiety and depression levels of pediatric MS patients and compare them with healthy controls. The average age of MS patients was 16.5 years, and 10 (66%) of the cases were women. The female/male ratio in our study was found to be similar to a prior study reporting that 67% of adolescent MS cases were female, and a previous review on pediatric MS reporting a ratio of 2.8:1 in children ≥12 years old (38,39). There are studies in the literature reporting that as the age of onset of MS decreases, the proportion of males increases, especially in children under the age of 10 (40). It is suggested that investigating the reasons for the change in the female/male ratio as the age decreases, especially in pediatric MS, may help further elucidate the pathophysiology of MS.

Different studies have demonstrated that cognitive functions may be impaired in children with pediatric MS (30,41,42). While many studies have examined cognitive function in pediatric MS patients using neuropsychological batteries, only a limited number of studies have formally evaluated academic achievement, which may ensure a better indication of future success (43,44). Evaluating academic achievement is a complex and multifaceted process that lacks a universally accepted standard. Moreover, determining the most influential variables that contribute to academic success is challenging, as different factors may play a more significant role for different individuals. Approximately 55% of all studies investigating academic achievement measure GPA as the primary outcome, and in our research, academic success was evaluated by asking parents about children's grade point averages (45). Similar to some of the previous studies, no significant difference was found between the MS group and healthy controls in terms of academic achievement (46). However, there are also studies showing that the academic achievement of children with MS is lower than the controls (47,48). More studies are needed to evaluate how pediatric MS affects the current and future academic achievement of children and adolescents.

No statistically significant difference was detected between the two groups regarding CDI scores, STAI state, and anxiety trait scores. This is one of the unexpected results of our study and is not similar to those reported mainly by studies in the literature. Studies in the literature mostly show that depression and anxiety symptoms are increased in pediatric MS patients (49,50). The fact that the depression and anxiety symptoms of children with MS in our sample were not different from the control group can be explained by the low rates of disability in our patient population. The average EDSS score of the pediatric MS patients included in our study was 0.33, indicating that the disability levels of the patient group are relatively low.

Table 1. Sociodemographic characteristics of groups

Sociodemographic variables	MS (n=15) Mdn (IQR)/n (%)	Control (n=15) Mdn (IQR)/n (%)	p-value
Gender[a]			
Female	10 (66.66)	6 (40)	0.143
Male	5 (33.33)	9 (60)	
Child's age (years)[b]	16.5 (14.5-18.5)	16.5 (15.5-17.5)	0.289
Mothers' age (years)[b]	47 (43.5-50.5)	41 (39-43)	0.132
Fathers' age (years)[b]	47 (45-49)	46 (33.5-48.5)	0.754
Mothers' education level[c], n (%)			
Primary school	3 (20)	2 (13.33)	0.294
Secondary school	6 (40)	3 (20)	
High school	4 (26.66)	3 (20)	
College degree or higher	2 (13.33)	7 (46.66)	
Mothers' occupation[a]			
Housewife	12 (80)	7 (46.66)	0.128
Full time employed	3 (20)	8 (53.33)	
Fathers' education level[c], n (%)			
Primary school	9 (60)	0 (0)	**0.001****
Secondary school	1 (6.66)	3 (20)	
High school	2 (13.33)	3 (20)	
College degree or higher	3 (20)	9 (60)	
Fathers' occupation			
Unemployed	1 (6.66)	0 (0)	1
Full time employed	14 (93.33)	15 (100)	
Number of siblings[b]	1 (0.5-1.5)	1 (0-2)	0.710
Family type[c], n (%)			
Nuclear family	10 (66.66)	13 (86.66)	0.390
Extended family	5 (33.33)	2 (13.33)	
Psychiatric diagnosis[c], n (%)			
Absent	15 (100)	12 (80)	0.224
Present	0 (0)	3 (20)	
Academic success[a], n (%)			
Average	7 (46.66)	8 (53.33)	0.133
High	8 (53.33)	7 (46.66)	
Absenteeism from school[a], n (%)			
<3 days	2 (13.33)	5 (33.33)	0.163
3-10 days	6 (40)	8 (53.33)	
>10 days	7 (46.66)	2 (13.33)	

Medians are shown with interquartile range in parantheses.

*p<0.05, **p<0.01, ***p<0.001

MS: Multiple sclerosis, Mdn: Median, IQR: Interquartile range

[a]Chi-square test, [b]Mann-Whitney U test, [c]Fisher's exact test

Table 2. Comparison of scale scores across the groups

Scales	MS (n=15) Mdn (IQR)	Control (n=15) Mdn (IQR)	Z/U	p-value
CDI	11 (10.5-11.5)	13 (10.5-15.5)	-1.71/71.5	0.087
STAI-C				
State anxiety	30 (18.5-41.5)	37 (30-44)	-0.02/112.0	0.983
Trait anxiety	43 (37.5-48.5)	38 (33.5-42.5)	-0.12/109.5	0.900

Medians are shown with interquartile range in parantheses.

*p<0.05, **p<0.01, ***p<0.001

MS: Multiple sclerosis, Mdn: Median, IQR: Interquartile range, CDI: Children's depression inventory, STAI-C: State-trait anxiety inventory for children

Mann-Whitney U test

Studies have shown a positive relationship between disability status and depression and anxiety levels in MS patients, and our results might be due to the fact that the patients have not yet developed disability and, therefore, have low EDSS levels (51).

Study Limitations

There are several limitations of our study. Firstly, since our study is cross-sectional, a longitudinal evaluation of depression and anxiety symptoms in children and adolescents with MS could not be performed. Secondly, in our study, self-rating scales were used to evaluate depression and anxiety levels, but no psychiatric examination was performed, and this may have caused various biases in the measurement of psychiatric symptoms. Finally, in our study, MS patients who applied to the clinic were evaluated, and the clinical sample used in the evaluation limits generalizability to the population.

Conclusion

Our study offers a nuanced understanding of the anxiety and depression levels of patients with pediatric MS as compared to healthy counterparts. The findings, especially regarding depression and anxiety symptoms, highlight the importance of considering individual variability and clinical characteristics in this population. As always, continuous research efforts in this area will help refine our understanding and offer a comprehensive perspective on the multifaceted effects of MS on pediatric populations.

Ethics

Ethics Committee Approval: The study was approved by the institutional ethics committee of Kocaeli University (no: 2023/265; date: 10.08.2023).

Informed Consent: Informed consent was obtained from all the participants and their parents after being provided with details regarding the study.

Authorship Contributions

Surgical and Medical Practices: S.D.B., G.Y.E., Concept: S.D.B., G.Y.E., Design: S.D.B., Data Collection or Processing: A.S.G., R.D.T., Analysis or Interpretation: R.D.T., Literature Search: S.D.B., Writing: S.D.B., G.Y.E.

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References

1. Boiko A, Vorobeychik G, Paty D, Devonshire V, Sadovnick D; University of British Columbia MS Clinic Neurologists. Early onset multiple sclerosis: a longitudinal study. Neurology 2002;59:1006-1010.
2. Ness JM, Chabas D, Sadovnick AD, Pohl D, Banwell B, Weinstock-Guttman B. Clinical features of children and adolescents with multiple sclerosis. Neurology 2007;68(16 Suppl 2):x37-45.
3. Banwell B, Krupp L, Kennedy J, Tellier R, Tenembaum S, Ness J, Belman A, Boiko A, Bykova O, Waubant E, Mah JK, Stoian C, Kremenchutzky M, Bardini MR, Ruggieri M, Rensel M, Hahn J, Weinstock-Guttman B, Yeh EA, Farrell K, Freedman M, Iivanainen M, Sevon M, Bhan V, Dilenge ME, Stephens D, Bar-Or A. Clinical features and viral serologies in children with multiple sclerosis: a multinational observational study. Lancet Neurol 2007;6:773-781.
4. Derle E, Kurne AT, Konuşkan B, Karabudak R, Anlar B. Unfavorable outcome of pediatric onset multiple sclerosis: Follow-up in the pediatric and adult neurology departments of one referral center, in Turkey. Mult Scler Relat Disord 2016;9:1-4.
5. Ghezzi A, Amato MP, Annovazzi P, Capobianco M, Gallo P, La Mantia L, Marrosu MG, Martinelli V, Milani N, Moiola L, Patti F, Pozzilli C, Trojano M, Zaffaroni M, Comi G; ITEMS (Immunomodulatory Treatment of Early-onset MS) Group. Long-term results of immunomodulatory treatment in children and adolescents with multiple sclerosis: the Italian experience. Neurol Sci 2009;30:193-199.
6. Waubant E, Chabas D. Pediatric multiple sclerosis. Curr Treat Options Neurol 2009;11:203-210.
7. Yeh EA, Chitnis T, Krupp L, Ness J, Chabas D, Kuntz N, Waubant E; US Network of Pediatric Multiple Sclerosis Centers of Excellence. Pediatric multiple sclerosis. Nat Rev Neurol 2009;5:621-631.
8. Boeschoten RE, Braamse AMJ, Beekman ATF, Cuijpers P, van Oppen P, Dekker J, Uitdehaag BMJ. Prevalence of depression and anxiety in Multiple Sclerosis: A systematic review and meta-analysis. J Neurol Sci 2017;372:331-341.
9. Fiest KM, Walker JR, Bernstein CN, Graff LA, Zarychanski R, Abou-Setta AM, Patten SB, Sareen J, Bolton JM, Marriott JJ, Fisk JD, Singer A, Marrie RA; CIHR Team Defining the Burden and Managing the Effects of Psychiatric Comorbidity in Chronic Immunoinflammatory Disease. Systematic review

and meta-analysis of interventions for depression and anxiety in persons with multiple sclerosis. Mult Scler Relat Disord 2016;5:12-26.

10. Feinstein A, O'Connor P, Gray T, Feinstein K. The effects of anxiety on psychiatric morbidity in patients with multiple sclerosis. Mult Scler 1999;5:323-326.
11. Chwastiak L, Ehde DM, Gibbons LE, Sullivan M, Bowen JD, Kraft GH. Depressive symptoms and severity of illness in multiple sclerosis: epidemiologic study of a large community sample. Am J Psychiatry 2002;159:1862-1868.
12. Patten SB, Beck CA, Williams JV, Barbui C, Metz LM. Major depression in multiple sclerosis: a population-based perspective. Neurology 2003;61:1524-1527.
13. Beiske AG, Svensson E, Sandanger I, Czujko B, Pedersen ED, Aarseth JH, Myhr KM. Depression and anxiety amongst multiple sclerosis patients. Eur J Neurol 2008;15:239-245.
14. Joffe RT, Lippert GP, Gray TA, Sawa G, Horvath Z. Mood disorder and multiple sclerosis. Arch Neurol 1987;44:376-368.
15. Siegert RJ, Abernethy DA. Depression in multiple sclerosis: a review. J Neurol Neurosurg Psychiatry 2005;76:469-475.
16. Nicholl CR, Lincoln NB, Francis VM, Stephan TF. Assessing quality of life in people with multiple sclerosis. Disabil Rehabil 2001;23:597-603.
17. Schiaffino KM, Shawaryn MA, Blum D. Examining the impact of illness representations on psychological adjustment to chronic illnesses. Health Psychol 1998;17:262-268.
18. Stenager E, Knudsen L, Jensen K. Multiple sclerosis: correlation of anxiety, physical impairment and cognitive dysfunction. Ital J Neurol Sci 1994;15:97-101.
19. Benedict RH, Hussein S, Englert J, Dwyer MG, Abdelrahman N, Cox JL, Munschauer FE, Weinstock-Guttman B, Zivadinov R. Cortical atrophy and personality in multiple sclerosis. Neuropsychology 2008;22:432-441.
20. Jones CD, Motl R, Sandroff BM. Depression in multiple sclerosis: Is one approach for its management enough? Mult Scler Relat Disord 2021;51:102904.
21. Feinstein A, Pavisian B. Multiple sclerosis and suicide. Mult Scler 2017;23:923-927.
22. Hopman WM, Coo H, Edgar CM, McBride EV, Day AG, Brunet DG. Factors associated with health-related quality of life in multiple sclerosis. Can J Neurol Sci 2007;34:160-166.
23. Ploughman M, Wallack EM, Chatterjee T, Kirkland MC, Curtis ME; Health Lifestyle and Aging with MS Consortium. Under-treated depression negatively impacts lifestyle behaviors, participation and health-related quality of life among older people with multiple sclerosis. Mult Scler Relat Disord 2020;40:101919.
24. Alschuler KN, Ehde DM, Jensen MP. The co-occurrence of pain and depression in adults with multiple sclerosis. Rehabil Psychol 2013;58:217-221.
25. Greeke EE, Chua AS, Healy BC, Rintell DJ, Chitnis T, Glanz BI. Depression and fatigue in patients with multiple sclerosis. J Neurol Sci 2017;380:236-241.
26. Raissi A, Bulloch AG, Fiest KM, McDonald K, Jetté N, Patten SB. Exploration of Undertreatment and Patterns of Treatment of Depression in Multiple Sclerosis. Int J MS Care 2015;17:292-300.
27. Feinstein A, Magalhaes S, Richard JF, Audet B, Moore C. The link between multiple sclerosis and depression. Nat Rev Neurol 2014;10:507-517.
28. Lester K, Stepleman L, Hughes M. The association of illness severity, self-reported cognitive impairment, and perceived illness management with depression and anxiety in a multiple sclerosis clinic population. J Behav Med 2007;30:177-186.
29. Mohr DC, Cox D. Multiple sclerosis: empirical literature for the clinical health psychologist. J Clin Psychol 2001;57:479-499.
30. Amato MP, Goretti B, Ghezzi A, Lori S, Zipoli V, Portaccio E, Moiola L, Falautano M, De Caro MF, Lopez M, Patti F, Vecchio R, Pozzilli C, Bianchi V, Roscio M, Comi G, Trojano M; Multiple Sclerosis Study Group of the Italian Neurological Society. Cognitive and psychosocial features of childhood and juvenile MS. Neurology 2008;70:1891-1897.
31. MacAllister WS, Belman AL, Milazzo M, Weisbrot DM, Christodoulou C, Scherl WF, Preston TE, Cianciulli C, Krupp LB. Cognitive functioning in children and adolescents with multiple sclerosis. Neurology 2005;64:1422-1425.
32. Weisbrot D, Charvet L, Serafin D, Milazzo M, Preston T, Cleary R, Moadel T, Seibert M, Belman A, Krupp L. Psychiatric diagnoses and cognitive impairment in pediatric multiple sclerosis. Mult Scler 2014;20:588-593.
33. Otallah S, Banwell B. Pediatric Multiple Sclerosis: an Update. Curr Neurol Neurosci Rep 2018;18:76.
34. Kovacs M. Children's depression inventory. Toronto Ontario, 1992.
35. Oy B. Depression rating scale of children: a validity and reliability study. J. Turk Psychaityr 1990;2:132-136.
36. Tomak L, Sarı M, Çavuş S, Bodur Güney HZ. Investigation of the factor structure of the Turkish version of the State-Trait Anxiety Inventory. Anatolian Clinic the Journal of Medical Sciences 2022.27:p.22-31.
37. Spielberger CD, Gorsuch RL, Lushene RE. STAI Manual for the Stait-Trait Anxiety Inventory ("Self-Evaluation Questionnaire"). Consulting Psychologists Press; 1970.
38. Aaen G, Waltz M, Vargas W, Makhani N, Ness J, Harris Y, Casper TC, Benson L, Candee M, Chitnis T, Gorman M, Graves J, Greenberg B, Lotze T, Mar S, Tillema JM, Rensel M, Rodriguez M, Rose J, Rubin J, Schreiner T, Waldman A, Weinstock-Guttman B, Belman A, Waubant E, Krupp L. Acquisition of Early Developmental Milestones and Need for Special Education Services in Pediatric Multiple Sclerosis. J Child Neurol 2019;34:148-152.
39. Jeong A, Oleske DM, Holman J. Epidemiology of Pediatric-Onset Multiple Sclerosis: A Systematic Review of the Literature. J Child Neurol 2019;34:705-712.
40. Chabas D, Strober J, Waubant E. Pediatric multiple sclerosis. Curr Neurol Neurosci Rep 2008;8:434-441.
41. Portaccio E, De Meo E, Bellinvia A, Amato MP. Cognitive Issues in Pediatric Multiple Sclerosis. Brain Sci 2021;11:442.
42. Amato MP, Krupp LB, Charvet LE, Penner I, Till C. Pediatric multiple sclerosis: Cognition and mood. Neurology 2016;87(9 Suppl 2):82-87.
43. Till C, Ghassemi R, Aubert-Broche B, Kerbrat A, Collins DL, Narayanan S, Arnold DL, Desrocher M, Sled JG, Banwell BL. MRI correlates of cognitive impairment in childhood-onset multiple sclerosis. Neuropsychology 2011;25:319-332.
44. Vargas WS, Noble KG, Banwell B, De Jager P. The educational impact of childhood-onset multiple sclerosis: Why assessing academic achievement is imperative. Mult Scler 2020;26:1633-1637.
45. York TT, C Gibson, S Rankin, Defining and measuring academic success. Practical Assessment, Research, and Evaluation 2015:20:p.5.
46. Boesen MS, Blinkenberg M, Thygesen LC, Eriksson F, Magyari M. School performance, psychiatric comorbidity, and healthcare utilization in pediatric multiple sclerosis: A nationwide population-based observational study. Mult Scler 2021;27:259-267.
47. Vargas W. Academic Underachievement is Common in Pediatric-Onset Multiple Sclerosis (P4-4.006). AAN Enterprises 2022
48. McKay KA, Friberg E, Razaz N, Alexanderson K, Hillert J. Long-term Socioeconomic Outcomes Associated With Pediatric-Onset Multiple Sclerosis. JAMA Neurol 2021;78:478-482.
49. Goretti B, Ghezzi A, Portaccio E, Lori S, Zipoli V, Razzolini L, Moiola L, Falautano M, De Caro MF, Viterbo R, Patti F, Vecchio R, Pozzilli C, Bianchi V, Roscio M, Comi G, Trojano M, Amato MP; Study Group of the Italian Neurological Society. Psychosocial issue in children and adolescents with multiple sclerosis. Neurol Sci 2010;31:467-470.
50. Bigi S, Banwell B. Pediatric multiple sclerosis. J Child Neurol 2012;27:1378-1383.
51. Seferoglu M. Factors Associated with Depression and Anxiety Severity in Multiple Sclerosis Patients. Journal of Multiple Sclerosis Research 2021;1:69-74.

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CASE REPORT

Effects of Aerobic Exercise on Restless Legs Syndrome Severity in Individuals with Multiple Sclerosis: A Case report

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Abstract

The primary focus in treating restless legs syndrome (RLS) is medical interventions. Although the benefits of physical activity are becoming increasingly evident, studies on the impact of exercise in people with both multiple sclerosis (MS) and RLS are limited. In this case report, we explored the effects of aerobic activity on RLS severity and related symptoms in a woman with RLS and MS. The RLS diagnostic criteria guided the diagnosis. Given the extensive impact of RLS symptoms, comprehensive assessment tools were utilized. Over 24 sessions, the patient performed aerobic exercise using a reclined exercise bike under the supervision of a physical therapist. Initially, each session lasted 20 min and consisted of 2-3 min of warm-up, 15 min of activity, and 2-3 min of cool-down. The duration of each session gradually increased to 30 min over 12 weeks. The study findings indicate that aerobic exercise may alleviate RLS severity, enhance sleep quality, reduce daytime sleepiness, improve gait, and enhance the quality of life in people with RLS and MS.

Keywords: Multiple sclerosis, restless legs syndrome, aerobic exercise, rehabilitation, sleep quality

Introduction

Multiple sclerosis (MS) is a chronic inflammatory condition that affects the central nervous system and causes diverse symptoms (1). Restless legs syndrome (RLS) commonly occurs in patients with MS (pwMS), affecting 13.3% and 65.1% of these patients (2). Despite its prevalence, RLS often goes unnoticed during neurological examinations, making its diagnosis and treatment challenging. Although medical interventions are traditionally preferred in the management of RLS, the increasing recognition of the benefits of exercise has prompted studies into the various forms of physical activity for patients with RLS. However, studies on exercise and its impact on RLS in pwMS are limited. In this case report, we aimed to explore the effects of aerobic exercise on RLS severity and related symptoms in a female patient diagnosed with both RLS and MS.

Case Report

A 42-year-old female initially presented to our MS center in 2013 with complaints of weakness. The patient was confirmed to have MS and treated with interferon beta-1b. In 2019, due to treatment inefficacy, fingolimod was discontinued and ocrelizumab was initiated. The severity of RLS symptoms was assessed using the RLS Rating Scale (RLSRS) (3). At the last routine visit, the patient scored 32 out of 40 on the RLS, indicating very severe symptoms despite ongoing medical treatment. Considering the limited efficacy of medical interventions, a collaborative decision was made by the physical therapist and neurologist to incorporate aerobic exercise in the patient's treatment regimen. With worsening RLS symptoms, even with medical treatment, aerobic exercise training was first introduced in August 2022. The first assessments were performed before initiating the 12-week personalized aerobic exercise program.

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Aerobic exercise was chosen as the therapeutic intervention on the basis of a protocol from previous RLS study. The exercise program involved a recumbent exercise bike and was conducted twice a week for 12 weeks under the supervision of a physical therapist. The exercise intensity was gradually increased from 60% to 75%. Each session initially lasted 20 min, consisting of 2-3 min of warm-up, 15 min of exercise, and 2-3 min of cool-down. The duration of each session was gradually increased until each session lasted 30 min at the end of 12 weeks. The patient's heart rate was monitored using a heart rate sensor (Polar H10). The patient completed all 24 sessions with high motivation and no adverse events.

RLS is diagnosed on the basis of five criteria outlined by the International RLS Working Group in 2014. The patient met all the criteria, and the RLS diagnosis was confirmed on June 29, 2019 (4). Comprehensive assessments were employed to evaluate various aspects affected by RLS symptoms before and after the 12-week aerobic exercise program. The assessments included the RLS severity (RLSRS score) (3), daytime sleeplessness (Epworth Sleepiness Scale) (5), sleep quality (Pittsburgh Sleep Quality Index) (6), walking speed (timed 25-foot walk test) (7), functional mobility (timed up and go test) (8), walking capacity (6-minute walk test) (7), quality of life (Multiple Sclerosis International Quality of Life) (9), and aerobic capacity (estimated VO_{2max}) (10). The results of these tests are presented in Table 1, and they demonstrate a 25% improvement in RLSRS scores and positive changes in all outcome measures. The patient signed a consent form for the publication of this report and the use their medical data.

Discussion

Managing RLS in pwMS includes diverse non-pharmacological methods such as infrared therapy, compression devices, exercise, and traditional acupuncture. However, the efficacy of these approaches remains debatable due to methodological shortcomings in current research (2). Evidence-based studies are urgently required to develop customized rehabilitation programs for such patients and identify their efficacy and optimal treatment duration. Despite the absence of robust evidence, numerous studies have suggested a potential reduction in RLS severity following aerobic exercise programs (11-13). Thus, we chose to implement aerobic exercises in our patient with both MS and RLS. The outcomes in our study suggest that aerobic exercises may alleviate RLS severity, improve daytime sleepiness and sleep quality, enhance gait, and elevate the quality of life.

Cederberg and Motl (14) explored the feasibility and effectiveness of physical activity modification in enhancing sleep outcomes and reducing RLS severity in pwMS. The 15 pwMS who had developed RLS and were included in the study were further divided into two groups: behavioral intervention (n=8) and control (n=7). The behavioral intervention method consisted of watching videos on a special website and attending 12 synchronous treatment sessions with a behavioral coach for 16 weeks. The participants were given a pedometer and asked to report their weekly step count on the special website. They reported enhancements in RLS severity, time in bed, sleep satisfaction, and sleep duration. They theorized that MS and RLS's shared pathways could benefit from the exercise-induced increase in dopaminergic signaling (14). The results in our patient support this idea. Our patient demonstrated a reduction in RLS severity and improvement in sleep symptoms and physical functions such as gait and estimated VO_{2max}. However, this mechanism should externally validated via randomized control trials with large sample sizes.

In conclusion, our case report demonstrates the impact of a 12-week aerobic exercise program on a woman with MS and RLS and highlights it's potential for enhancing overall health. The results indicate the need to consider RLS symptoms alongside MS symptoms and understand how MS symptoms may affect the assessment and intervention of such patients. The favorable study results suggest the need for thorough randomized controlled trials on aerobic exercise in pwMS and RLS, which could offer valuable insights and validate its benefits. Although

Table 1. Outcomes of the patient before and after the 12-week aerobic exercise program

	Before the program	After the program	Percentage of change
RLSRS (0-40 points)	32	24	25%
ESS (0-24 points)	13	6	54%
PSQI (0-21 points)	11	8	27%
T25FW (sec)	8.74	8.66	1%
TUG (sec)	16.57	15.13	9%
6-MWT (meter)	240	321	34%
MusiQoL (0-100 points)	33.22	42.25	27%
Estimated VO_{2max} (mL/kg/min)	38.10	42.00	10%

RLSRS: RLS Rating Scale, ESS: Epworth Sleepiness Scale, PSQI: Pittsburgh Sleep Quality Index, T25FW: Timed 25-foot walk, TUG: Timed up and go, 6-MWT: 6-minute walk test, MusiQoL: Multiple Sclerosis International Quality of Life

this case report demonstrates that aerobic exercise can improve RLS symptoms, the findings cannot be generalized to pwMS or other neurological conditions.

Ethics

Informed Consent: Informed consent was obtained from patients.

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

REFERENCES

1. Hunter SF. Overview and diagnosis of multiple sclerosis. Am J Manag Care 2016;22:s141-150.
2. Ozdogar AT, Kalron A. Restless legs syndrome in people with multiple sclerosis: An updated systematic review and meta-analyses. Mult Scler Relat Disord 2021;56:103275.
3. Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, Trenkwalder C; International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med 2003;4:121-132.
4. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, Zucconi M, Ferri R, Trenkwalder C, Lee HB; International Restless Legs Syndrome Study Group. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria--history, rationale, description, and significance. Sleep Med 2014;15:860-873.
5. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-545.
6. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213.
7. Scalzitti DA, Harwood KJ, Maring JR, Leach SJ, Ruckert EA, Costello E. Validation of the 2-Minute Walk Test with the 6-Minute Walk Test and Other Functional Measures in Persons with Multiple Sclerosis. Int J MS Care 2018;20:158-163.
8. Sebastião E, Sandroff BM, Learmonth YC, Motl RW. Validity of the Timed Up and Go Test as a Measure of Functional Mobility in Persons With Multiple Sclerosis. Arch Phys Med Rehabil 2016;97:1072-1077.
9. 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.
10. Legge BJ, Banister EW. The Astrand-Ryhming nomogram revisited. J Appl Physiol (1985) 1986;61:1203-1209.
11. Aukerman MM, Aukerman D, Bayard M, Tudiver F, Thorp L, Bailey B. Exercise and restless legs syndrome: a randomized controlled trial. J Am Board Fam Med 2006;19:487-493.
12. Mortazavi M, Vahdatpour B, Ghasempour A, Taheri D, Shahidi S, Moeinzadeh F, Dolatkhah B, Dolatkhah S. Aerobic exercise improves signs of restless leg syndrome in end stage renal disease patients suffering chronic hemodialysis. ScientificWorldJournal 2013;2013:628142.
13. Xu XM, Liu Y, Jia SY, Dong MX, Cao D, Wei YD. Complementary and alternative therapies for restless legs syndrome: An evidence-based systematic review. Sleep Med Rev 2018;38:158-167.
14. Cederberg KLJ, Motl RW. Feasibility and efficacy of a physical activity intervention for managing restless legs syndrome in multiple sclerosis: Results of a pilot randomized controlled trial. Mult Scler Relat Disord 2021;50:102836.

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