Case Report

Assessing Muscle Fatigue in Multiple Sclerosis using the Sample Entropy of Electromyographic Signals: A Proof of Concept

Marina Gomez-Hernández[1], **Natali Olaya-Mira**[2], **Carolina Viloria-Barragán**[2], **Julieta Henao-Pérez**[3], **Jessica María Rojas-Mora**[1], **Gloria Díaz-Londoño**[4]

[1]Faculty of Exact and Applied Sciences, Metropolitan Technological Institute, Medellín, Colombia, [2]Biomedical Research and Innovation Group (GI2B), Faculty of Exact and Applied Sciences, Metropolitan Technological Institute, Medellín, Colombia, [3]Cooperative University of Colombia, Faculty of Health Sciences, Medicine, Medellín and Envigado, [4]National University of Colombia – Medellín Campus, Faculty of Sciences, School of Physics, Radiological Physics Research Group, Medellín, Colombia

Abstract

Background: Multiple sclerosis (MS) is a progressive and neurodegenerative disease of the central nervous system. Its symptoms vary greatly, which makes its diagnosis complex, expensive, and time-consuming. One of its most prevalent symptoms is muscle fatigue. It occurs in about 92% of patients with MS (PwMS) and is defined as a decrease in maximal strength or energy production in response to contractile activity. This article aims to compare the behavior of a healthy control (HC) with that of a patient with MS before and after muscle fatigue. **Methods:** For this purpose, a static baropodometric test and a dynamic electromyographic analysis are performed to calculate the area of the stabilometric ellipse, the remitting MS (RMS) value, and the sample entropy (SampEn) of the signals, as a proof of concept to explore the feasibility of this test in the muscle fatigue quantitative analysis; in addition, the statistical analysis was realized to verify the results. **Results:** According to the results, the ellipse area increased in the presence of muscle fatigue, indicating a decrease in postural stability. Likewise, the RMS value increased in the MS patient and decreased in the HC subject and the opposite behavior in the SampEn was observed in the presence of muscle fatigue. **Conclusion:** Thus, this study demonstrates that SampEn is a viable parameter to estimate muscle fatigue in PwMS and other neuromuscular diseases.

Keywords: *Baropodometry, electromyography, multiple sclerosis, muscle fatigue, sample entropy*

Submitted: 15-Dec-2021 **Revised:** 02-Jul-2022 **Accepted:** 10-Aug-2022 **Published:** 29-May-2023

Introduction

Multiple sclerosis (MS) is a neurodegenerative disease of the central nervous system, characterized by being progressive because damage spreads throughout the brain and spinal cord. It may cause physical or cognitive disability, as well as neurological problems in young adults.[1] About 85%–90% of patients with MS (PwMS) have a relapsing-remitting course of the disease.[2] Relapsing-remitting MS (RRMS) is characterized by relapses or flare-ups that may have different durations and intensity of the symptoms and often result in transition to secondary-progressive MS (SPMS).[3-5]

MS affects women more than men, and its prevalence varies around the globe[6-8] In Colombia, for instance, its prevalence ranges from 1 to 16/100,000 inhabitants,[9] which is why it was classified as an orphan disease according to Resolution 5265 of 2018 by the Ministry of Health and Social Protection.

The symptoms of MS vary greatly, which can cause it to be mistaken for other diseases. Currently, there are no clinical findings or complementary tests that allow its accurate diagnosis[10-13] which makes its diagnosis complex, expensive, and time-consuming[14,15]

Some authors have studied the symptoms experienced by PwMS before being diagnosed. For this purpose, they have analyzed the medical records of the 5 years prior to the occurrence of the first demyelinating event and have found that the most prevalent symptoms include pain, sleep disorders, anemia, and fatigue.[16]

Up to 92% of PwMS may experience fatigue,[17] which has been defined as the lack of physical or mental energy to carry out daily living activities[18] and estimated based on the perception of patients or caregivers. Some studies have been developed to evaluate fatigue depending on the symptoms displayed by PwMS.[19] Muscle fatigue has been particularly quantified

How to cite this article: Gomez-Hernández M, Olaya-Mira N, Viloria-Barragán C, Henao-Pérez J, Rojas-Mora JM, Díaz-Londoño G. Assessing muscle fatigue in multiple sclerosis using the sample entropy of electromyographic signals: A proof of concept. J Med Sign Sens 2023;13:153-9.

Address for correspondence:
Dr. Carolina Viloria-Barragán,
Carrera 76A # 32A - 73,
Medellín, Colombia.
E-mail: carolinaviloria@itm.edu.co

Access this article online

Website: www.jmssjournal.net

DOI: 10.4103/jmss.jmss_184_21

Quick Response Code:

using surface electromyography (sEMG) in healthy controls (HCs) and PwMS. The latter have been found to exhibit greater muscle fatigue during walking, a symptom associated with the disease.[20]

Moreover, sEMG signals of the upper and lower limbs in PwMS have been processed to obtain more specific data, such as average rectified value, mean frequency of the power spectrum, muscle fiber conduction velocity, and fractal dimension, which have been used as indirect indicators of muscle fatigue, particularly in the biceps brachii.[21]

Among these specific data, the sample entropy (SampEn) of sEMG signals stands out, making it possible to quantify the complexity and randomness of a dynamic system represented by a time series. This measure reflects the state of a given signal from a new perspective in the nonlinear complexity domain rather than in the conventional time or frequency domains.[22]

According to the above, analyzing muscle fatigue in PwMS through sEMG signal processing can provide more information for the diagnosis and follow-up of this complex disease. Therefore, this study seeks to develop a proof of concept for evaluating muscle fatigue using baropodometry and sEMG signal processing to analyze the root mean square (RMS) value and the SampEn of the signals and determine whether these two characteristics significantly differ between a HC and a PwMS. The aim is to provide data that can help to conduct specific rehabilitation programs, considering the heterogeneity of the demyelinating lesions and their different and unique patterns in each patient.[23]

Methods

Muscle fatigue was quantified under static and dynamic conditions using baropodometry and sEMG (during walking), respectively. Participants included a female PwMS (body mass index [BMI] = 20.6) and a female HC (BMI = 20.3) with similar physical characteristics. The measurements were obtained in the Biomechanics and Rehabilitation Laboratory at the Instituto Tecnológico Metropolitano.

Inclusion criteria

The HC was an adult woman with no motor impairments and no medical history. The PwMS met the following inclusion criteria: (a) an MS diagnosis clinically defined as RRMS-SPMS according to McDonald's criteria, (b) age over 18 years (46 years old), (c) a score from 0 to 3.5 in the expanded disability status scale,[24] and (d) no history of other diseases affecting the musculoskeletal system, or heart or respiratory conditions. In addition, such subjects did not meet any of the exclusion criteria, which included: (a) being pregnant, (b) having had a MS relapse in the 3 months prior to the study, and (c) not being willing to provide written informed consent.[20,25-27] The study protocol was approved by the Ethics Committee of the Instituto Tecnológico Metropolitano.

Signal acquisition

Baropodometry

The baropodometric analysis was performed using the EcoWalk plantar pressure plate (Ecosanit, Arezzo, Italy). This system consists of a portable plate and a 480 mm × 480 mm active matrix with 2,304 sensors. Its data acquisition frequency is 40 (noninterpolated) frames per second. In addition, it has 4100 color levels that represent the pressure levels detected mathematically. The sensors activated by each foot provide data for the identification and calculation of baropodometric variables such as body weight distribution and area of the stabilometric ellipse.[28]

To perform this test, a marker which serves as a visual reference point must be fixed to the wall at the subject's eye level. Subjects are placed on the plantar pressure plate, making sure that: (a) both feet are on the plate, separated by a distance equal to the width of the shoulders, and (b) the image projected on the computer completely shows the plantar surface. Subjects must remain in this position for 60 s, which is the time the EcoFoot software takes to acquire the information. Measurements were taken before gait initiation and after muscle fatigue occurred.

Electromyography

Signals were obtained using sEMG, which is a technique that captures and measures electrical activity and changes in the action potential of muscles while at rest or during the performance of some activity.[29]

FREEEMG (BTS Bioengineering, Milan, Italy), a sEMG device with wireless probes for the dynamic analysis of muscle activity, was used. Besides being compact (41.5 mm × 24.8 mm × 14 mm) and lightweight (13 gr/probe), this device wirelessly transmits data (IEEE 802.15.4) to a PC through USB receivers (2.0). Each probe is equipped with internal memory to ensure uninterrupted recording in case of temporary connection loss.

For the analysis of muscle fatigue during walking, electrodes were placed on the subjects' tibialis Anterior (TA), medial gastrocnemius (MG), lateral gastrocnemius (LG), rectus femoris (RF), vastus medialis (VM), vastus lateralis (VL), semitendinosus (ST), and biceps femoris (BF) muscles [Figure 1]. In the PwMS, they were placed on the left lower limb, as it is the most affected by this disease. In the HC, they were placed on the right lower limb because this was her dominant leg.

For electrode placement, subjects' skin was prepared, and participants adopted different postures to facilitate the identification of the muscles and, thus, determine the correct location of the probes. Ag/AgCl electrodes with a conductive area not exceeding 10 mm^2 were used, and the inter-electrode distance was 20 mm. Electrodes were selected and placed in accordance with the Surface EMG Non-Invasive Assessment of Muscles protocol.[30]

Subsequently, subjects were instructed to walk on a treadmill at a self-selected speed. sEMG signals were recorded for 60 s at two different moments: (1) after a warm-up and (2) after showing signs of muscle fatigue.

Signal analysis

Baropodometry

The sway of the body's center of gravity in presence or absence of muscle fatigue was analyzed by calculating the area of the stabilometric ellipses using the EcoFoot software (Ecofoot software (version 4.0), Ecosanit, Arezzo, Italy), as an increase in such area is associated with a decrease in body stability [Figure 2].[31]

Electromyography

For signal analysis, variables such as RMS value, whose increase is associated with the presence of muscle fatigue in MS patients,[20] and SampEn, which assesses the complexity of signals,[32] were calculated.

Root mean square value

This time analysis feature is widely used in the analysis of electromyographic signals because its result is directly associated with the amplitude of a given signal, which allows muscle electrical activity to be detected more clearly. Given a time series {X1...., XN}, the RMS value can be calculated using the following equation:[33]

$$RMS = \sqrt{\frac{1}{N}\sum_{i=1}^{N} X_i^2}$$

Where RMS denotes the RMS value of the original signal and *N*, its length.

Sample entropy

The complexity of signals can be evaluated using different metrics, such as the SampEn algorithm,[34,35] SampEn is used to estimate the regularity of physiological signals (including sEMG signals) for the evaluation of the properties of biological systems.[36] It is defined as the negative natural logarithm of the conditional probability that subseries of length *m*, which match pointwise within a tolerance *r*, will also match at point m + 1. In addition, it assesses the nonlinear predictability of signals. To calculate the SampEn of a given time series {x1..., xN}, the following equations[37] are used:

$$SampEn(m,r,N) = -ln\left[\frac{U^{m+1}(r)}{U^{m}(r)}\right] \tag{1}$$

$$U^{m}(r) = [N - m\tau]^{-1}\sum_{i=1}^{N-m\tau} C_i^m(r) \tag{2}$$

Where $C_i^m(r) = \dfrac{B_i}{(N-(m+1)\tau)}$ (3)

Where $B_i = number\ of\ j\ where\ d\left|X_i, X_j\right| \leq r$

$$X_i = \left(X_i\ , X_{i+\tau} \ldots, X_{i+(m-1)\tau}\right)$$

$$X_j = \left(X_j\ , X_{j+\tau} \ldots, X_{j+(m-1)\tau}\right) \quad i \leq j \leq N - m\tau\ , j \neq i$$

Here, *N* is the total length of the observed time series; *m*, the embedding dimension; *r*, the tolerance factor (for which two subseries with a distance below its value are considered identical); and τ, the time delay expressed in the samples.

In this study, MATLAB software (version 2020. b) was employed to calculate the SampEn of the signals, considering the following parameters: $M = 2$, $\tau = 1$, and $r = 0.25 \times$ standard deviation (SD), where SD is the SD of the signal. These parameters are commonly used to analyze the complexity of biological signals.[35]

Statistical method

From the RMS and Entropy values obtained for each muscle under consideration, from the HC and the PwMS, Bayesian methods were used to characterize the individual behavior of the differences and make comparisons between the data. Since, it allows to inference from the evidence observed in the data using Bayes' theorem.[38-40]

The procedure used to compare the two subjects (HC and PwMS) states is called BEST (Bayesian estimation supersedes the *t*-test). This alternative to *t*-test produces posterior estimates for the means and SDs of the groups and their differences and effect sizes. Characterization was performed based on three parameters of interest: mean, SD, and freedom degrees, with the BESTmcmc function of the BEST package from R software (4.1.3). The BEST assumes that the generative model for the data is a t-distribution; in this case, the data points may be outliers to some degree.[41]

Results

This section shows the results obtained for the PwMS and the HC. For the baropodometric analysis, we present the estimated areas of the stabilometric ellipses and, for the electromyography analysis, the estimated RMS and SampEn values of the signal of each muscle.

Baropodometry

From the baropodometric analysis without muscle fatigue, we obtained an area of 56.49 mm^2 and 660.49 mm^2 for the HC and the PwMS, respectively. However, in the presence of muscle fatigue, those areas increased in both subjects: 77.78 mm^2 (HC) and 2,576.63 mm^2 (PwMS). As observed, this area is greater in the PwMS in both cases.

Electromyography

Figures 3 and 4 show the RMS and SampEn results for the HC (circle) and PwMS (triangle). Absence of muscle fatigue (red) and presence of muscle fatigue (black).

In the HC, it decreased in factors between 0.126 and 0.992, with the ST muscle exhibiting the greatest increase. In the PwMS, it increased between 1.064 and 5.556 times, except in the ST muscle, which showed a decrease in the RMS value in the presence of muscle fatigue. In the PwMS, variation in this value is minimal for the BF muscle.

In the HC, it increased between 1.009 and 1.956 times, with the ST muscle exhibiting the greatest increase. In the PwMS, it decreased in factor between 0.470 and 0.990, except in the ST muscle, which showed an increase in the SampEn value in the presence of muscle fatigue.

Statistical analysis

For each of the muscles of interest, the RMS of the patients in the following situations is compared:

- HC, before and after performing the physical activity
- PwMS, before and after performing the physical activity
- PwMS and HC, before performing the physical activity
- PwMS and HC, after physical activity.

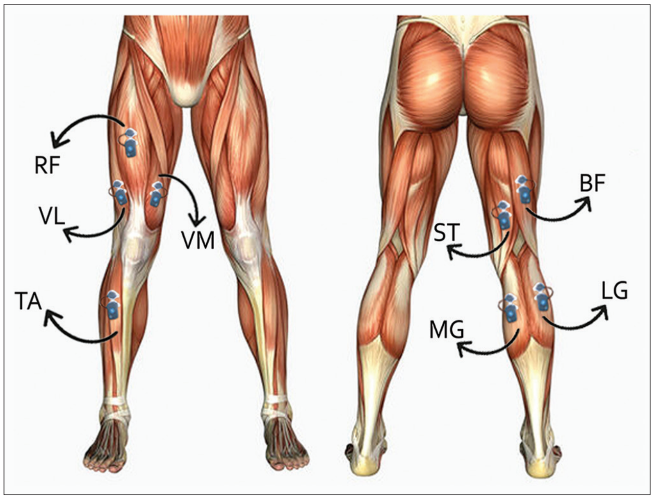

Figure 1: Probe placement on muscles. Source: Authors' own work

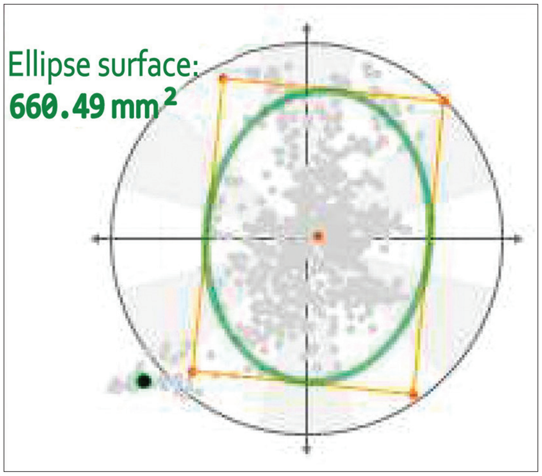

Figure 2: Area of the stabilometric ellipses calculated based on the sway of the body's center of gravity while standing

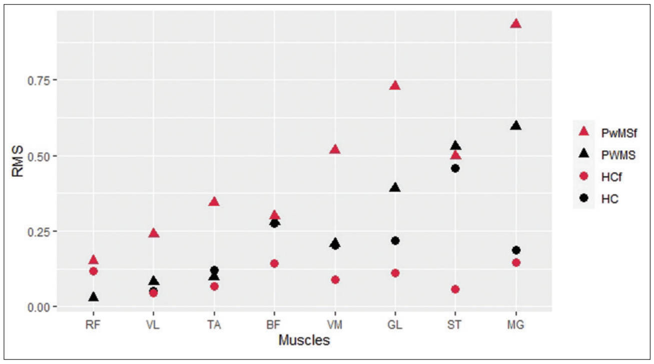

Figure 3: RMS values for the PwMS and the HC in presence and absence of muscle fatigue

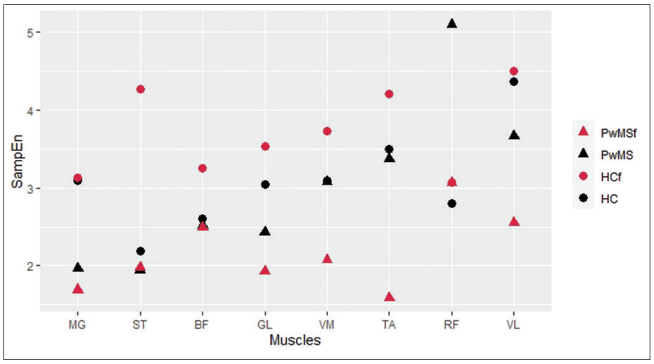

Figure 4: Sample entropy values of the signals obtained from the patient with multiple sclerosis and the healthy control in presence and absence of muscle fatigue

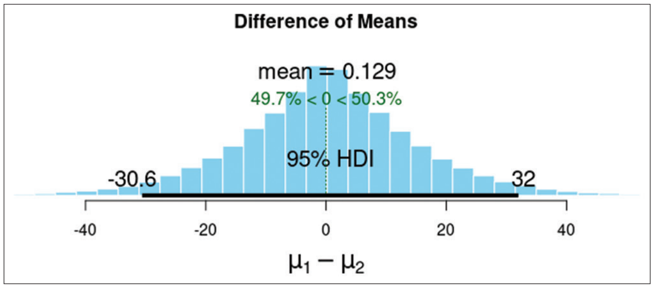

Figure 5: Posterior probability distribution for the difference of the RMS values in the RF muscle, RMS: Remitting multiple sclerosis, RF: Rectus femoris

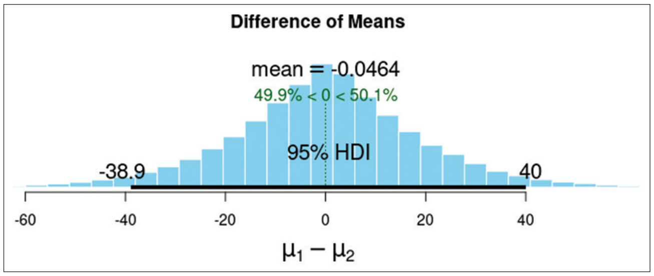

Figure 6: Posterior probability distribution for the difference of the RMS values in the GM muscle, RMS: Remitting multiple sclerosis, GM: Gluteus maximus

Bayesian analysis was performed for the difference in the observed values. A posterior distribution density plot shows the credibility interval at 95% and the under curve area for the difference around the null value. The results for the RF and MG muscles are presented in Figures 5 and 6, respectively.

When performing the difference between the RMS values obtained in the RF muscle of the PwMS with respect to the healthy patient, it was found that the difference is 0.15. By estimating the parameters of the Bayesian model, the posterior probability distribution for the difference of the RMS values is shown in Figure 5, in which a value of 0.129 is observed for the posterior mean, which is lower than the observed point value. The 95% credible interval for the difference corresponds to (−30.6; 32) and the probability of observing a null difference between the two values of interest ranges from 49.7% to 50.3%.

The difference between the RMS values obtained in the GM muscle of the PwMS with respect to the healthy patient takes a negative value, indicating a higher RMS value in the healthy patient. By estimating the parameters of the Bayesian, the posterior probability distribution for the difference of the RMS values is shown in Figure 6, in which a value of 0.0464 is observed for the posterior mean, which is lower than the observed point value. The 95% credible interval for the difference corresponds to (−38.9; 40) and the probability of observing a null difference between the two values of interest ranges from 49.9% to 50.1%.

Discussion

Baropodometry

The area of the stabilometric ellipses before and during muscle fatigue was found to be greater in the PwMS than in the HC. For instance, before muscle fatigue, it was 11.69 times greater in the PwMS than in the HC, whereas, during muscle fatigue, such area in the HC was 33.13 times lower than observed in the PwMS, which suggests that this latter has less body stability. In addition, the area of the ellipses increased in both subjects in the presence of muscle fatigue, thus confirming its existence, as it results in a decrease in postural stability. This finding is supported by previous studies, which have reported that muscle fatigue is associated with postural stability, mainly in PwMS.[42-44]

Electromyography

In the PwMS, the increase in the RMS value of the electromyographic signals observed in Figure 3 could be associated with the presence of muscle fatigue, which is in line with what has been reported in similar studies.[20] However, the ST muscle showed a different behavior in which the RMS value decreased during muscle fatigue. This could be related to this patient's difficulty in bending the knee, as this muscle is directly involved in the said movement.[45,46] In the HC was observed a decrease in the RMS value of the electromyographic signal. Therefore, the behavior of RMS value between HC and PwMS is different. This result may help identify when a patient suffers from a muscle disorder that can have MS or other diseases.

In the PwMS, most of the SampEn values without fatigue were higher than with fatigue, except in ST and BF; the behavior without fatigue may be attributed to an impaired activation of the motor neurons that drive muscle fibers. This impairment, in turn, is due to alterations in the transmembrane ionic concentrations that limit the firing of the action potentials that affect the perceived sEMG signal,[43] which may manifest as an increase in the complexity of the signal. The action potentials in the membrane are generated when there is muscle activation. In this case, the exercise causes a constant activation, and the behavior randomly of signals can decrease; therefore, the SampEn decreases in the case of fatigue. In the PwMS, it is recommended to do exercises to control the symptoms, and it is possible that the action potentials were more stable with constant activation.

Some similar studies examined the differences in the activation patterns of the ST and BF muscles and reported conflicting results. However, the increase in the electromyographic activity of the BF muscle has been suggested to be an attempt of the neuromuscular system to contract the already stretched muscle fascicles,[41] which could explain the different behaviors of the ST and BF muscles in terms of SampEn in the PwMS.

In the HC, most of the SampEn values without fatigue were lower than with fatigue, and the principal differences were observed in ST and BF. The randomness in the signals is lower without fatigue because there is no delay in propagation velocity. With fatigue, muscle activation is generated and the action potentials may be more random.

The SampEn of the electromyographic signals obtained before muscle fatigue was found to be lower in the PwMS than in the HC in most muscles, because the PwMS has a demyelination and axonal neurodegeneration disorder that alters ion channels and membrane potentials, which may manifest as a decrease in the complexity of the signal.[44,45]

SampEn is currently being used in the analysis of biological signals to evaluate physiological characteristics and study neuromuscular disorders,[37] regardless of the processing of the signal, thus making it invariant to the noise captured during signal acquisition.[36]

Finally, this proof of concept shows the feasibility of using SampEn to estimate muscle fatigue in PwMS. Therefore, future work should concentrate on studying several MS patients with different demyelinating lesions that affect other muscle groups and that can be correlated with the diagnosis and follow-up of this disease.

Acknowledgement

The authors would like to thank the Laboratorio de Biomecánica y Rehabilitación of the Instituto Tecnológico Metropolitano in Medellín for providing the infrastructure and the assistant staff to conduct this study. We would like to thank Universidad Nacional de Colombia, the Medellín campus, for the support given to obtain the Matlab licenses needed to develop the codes in this work. The authors would like to thank Universidad Cooperativa de Colombia, medicine faculty, for their assistance in the inclusion criteria.

Financial support and sponsorship

This research was funded by Instituto Tecnológico Metropolitano, grant number P20251, and Universidad Nacional de Colombia, grant number 50859.

Conflicts of interest

There are no conflicts of interest.

References

1. Ghasemi N, Razavi S, Nikzad E. Multiple sclerosis: Pathogenesis, symptoms, diagnoses and cell-based therapy. Cell J 2017;19:1-10.
2. Goodin DS. The Epidemiology of Multiple Sclerosis: Insights to a Causal Cascade. In: Handbook of Clinical Neurology. 1st ed., Vol. 138. no. 3. Amsterdam: Elsevier B.V., 2016.
3. Nogales-Gaete J, Aracena R, Cepeda-Zumaeta S, Eloiza C, Agurto P, Díaz V, *et al.* Clinical features of 314 patients with relapsing-remitting multiple sclerosis. Rev Med Chil 2014;142:559-66.
4. Osorio-Marcatinco V, Castro-Suarez S, Meza-Vega M. Cognitive characteristics of patients with relapsing - remitting multiple sclerosis during relapse attended in National Institute of Neurological Sciences 2014 - 2016. Rev Neuropsiquiatr 2018;81:58-64.
5. Oh J, Alikhani K, Bruno T, Devonshire V, Giacomini PS, Giuliani F, *et al*. Diagnosis and management of secondary-progressive multiple sclerosis: Time for change. Neurodegener Dis Manag 2019;9:301-17.
6. Olek M, Mowry E. Pathogenesis and epidemiology of multiple sclerosis," Up To Date; 2020. p. 1-23. Available: https://www.uptodate.com/contents/pathogenesis-and-epidemiology-of-multiple-sclerosis. [Last cited on 2020 May 06].
7. Leray E, Moreau T, Fromont A, Edan G. Epidemiology of multiple sclerosis. Rev Neurol (Paris) 2016;172:3-13.
8. Negrotto L, Correale J. Evolution of multiple sclerosis prevalence and phenotype in Latin America. Mult Scler Relat Disord 2018;22:97-102.
9. Jiménez C, Zarco L, Castañeda C, Otálora M, Martínez A, Rosselli D. Current state of multiple sclerosis in Colombia. Acta Neurol Colomb 2015;31:385-90.
10. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, *et al*. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162-73.
11. Diazgranados Sánchez JA, Burbano J, Herrera Escandón Á, Hidalgo JF, Gómez Betancourt LF, Chan Guevara L. Mc Donald 2010 criteria in the diagnosis of multiple sclerosis in Cali, Colombia. Acta Neurol Colomb 2013;29:247-54.
12. Jarmi V, De Elías R, Kiener O, Villate S, Vrech C, Barzón S. Oligoclonal bands: contribution and interpretation in patients with suspected multiple sclerosis. Acta Bioquim Clin Latinoam 2015;49:257-65.
13. Rojas Huerto E, Alva Diaz C, Montalvan Ayala V. Clinical changes of multiple sclerosis according to modification of the McDonald criteria. Hospital Almenara, 2001-2015. An la Fac Med 2019;80:34-8.
14. Martinez-Altarriba MC, Ramos-Campoy O, Luna-Calcaño IM, Arrieta-Antón E. A review of multiple sclerosis (2). Diagnosis and treatment. Semergen 2015;41:324-8.
15. Castellano-Del Castillo MA, Lacasa-Andrade ME, Hijós-Bitrián E, Mambrona-Girón L, Sebastiá-Vigatá E, Vázquez-Sasot A. Effectiveness of rehabilitation in multiple sclerosis. Rehabilitacion 2014;48:46-53.
16. Yusuf F, Wijnands JM, Kingwell E, Zhu F, Evans C, Fisk JD, *et al*. Fatigue, sleep disorders, anaemia and pain in the multiple sclerosis prodrome. Mult Scler 2021;27:290-302.
17. Proessl F, Poston B, Rudroff T. Does a single application of anodal tDCS improve knee extensor fatigability in people with multiple sclerosis? Brain Stimul 2018;11:1388-90.
18. Newland P, Van Aman MN, Smith J, Spencer A. Relationship of fatigue to heat sensitivity in patients with multiple sclerosis: A review for management. J Nurse Pract 2018;14:100-4.
19. Sumowski JF, Leavitt VM. Body temperature is elevated and linked to fatigue in relapsing-remitting multiple sclerosis, even without heat exposure. Arch Phys Med Rehabil 2014;95:1298-302.
20. Eken MM, Richards R, Beckerman H, van der Krogt M, Gerrits K, Rietberg M, *et al*. Quantifying muscle fatigue during walking in people with multiple sclerosis. Clin Biomech (Bristol, Avon) 2020;72:94-101.
21. Beretta-Piccoli M, Cescon C, Barbero M, Villiger M, Clijsen R, Kool J, *et al*. Upper and lower limb performance fatigability in people with multiple sclerosis investigated through surface electromyography: A pilot study. Physiol Meas 2020;41:025002.
22. Zhang X, Wang D, Yu Z, Chen X, Li S, Zhou P. EMG-torque relation in chronic stroke: A novel EMG complexity representation with a linear electrode array. IEEE J Biomed Health Inform 2017;21:1562-72.
23. Lucchinetti C, Bruck W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: Implications for the pathogenesis of demyelination. Ann Neurol 2000;47:707-17.
24. Conradsson D, Ytterberg C, Engelkes C, Johansson S, Gottberg K. Activity limitations and participation restrictions in people with multiple sclerosis: A detailed 10-year perspective. Disabil Rehabil 2021;43:406-13.
25. Goldman MD, Marrie RA, Cohen JA. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. Mult Scler 2008;14:383-90.
26. Hayes S, Uszynski MK, Motl RW, Gallagher S, Larkin A, Newell J, *et al*. Randomised controlled pilot trial of an exercise plus behaviour change intervention in people with multiple sclerosis: The Step it Up study. BMJ Open 2017;7:e016336.
27. Thomas S, Fazakarley L, Thomas PW, Collyer S, Brenton S, Perring S, *et al.* Mii-vitaliSe: a pilot randomised controlled trial of a home gaming system (Nintendo Wii) to increase activity levels, vitality and well-being in people with multiple sclerosis. BMJ Open 2017;7:e016966.
28. Zequera M, Perdomo O, Wilches C, Vizcaya P. Pilot study: Assessing repeatability of the EcoWalk platform resistive pressure sensors to measure plantar pressure during barefoot standing. J Phys Conf Ser 2013;50:1-4.

29. Fukuda TY, Echeimberg JO, Pompeu JE, Garcia-Lucareli PR, Garbelotti S, Okano-Gimenes R, *et al*. Root mean square value of the electromyographic signal in the isometric torque of the quadriceps, hamstrings and brachial biceps muscles in female subjects. J Appl Res 2010;10:32-9.
30. Hermens HJ, Freriks B, Disselhorst-Klug C, Rau G. Development of recommendations for SEMG sensors and sensor placement procedures. J Electromyogr Kinesiol 2000;10:361-74.
31. Petrocci KE, Cárdenas Sandoval RP. La medición del control postural con estabilometría- una revisión documental. Rev Colomb Rehabil 2011;10:16-24.
32. Richman J, Lake D, Moorman JR. Sample entropy. Methods Enzymol 2004;384:172-84.
33. Phinyomark A, Phukpattaranont P, Limsakul C. Feature reduction and selection for EMG signal classification. Expert Syst Appl 2012;39:7420-31.
34. Perpetuini D, Cardone D, Chiarelli AM, Filippini C, Croce P, Zappasodi F, *et al*. Autonomic impairment in Alzheimer's disease is revealed by complexity analysis of functional thermal imaging signals during cognitive tasks. Physiol Meas 2019;40:1-9.
35. Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. Am J Physiol Heart Circ Physiol 2000;278:H2039-49.
36. Zhang X, Zhou P. Sample entropy analysis of surface EMG for improved muscle activity onset detection against spurious background spikes. J Electromyogr Kinesiol 2012;22:901-7.
37. Perpetuini D, Chiarelli AM, Cardone D, Filippini C, Bucco R, Zito M, *et al*. Complexity of frontal cortex fNIRS can support Alzheimer disease diagnosis in memory and visuo-spatial tests. Entropy (Basel) 2019;21:E26.
38. Berger JO. Statistical Decision Theory and Bayesian Analysis. New York: Springer; 1985.
39. Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A, Rubin DB. Bayesian Data Analysis. New York: Chapman and Hall/CRC; 2013.
40. Bolstad WM. Introduction to Bayesian Statistics. New Jersey: John Wiley & Sons; 2004.
41. Kruschke JK. Bayesian estimation supersedes the *t*-test. J Exp Psychol Gen 2013;142:573-603.
42. Arpan I, Fino PC, Fling BW, Horak F. Local dynamic stability during long-fatiguing walks in people with multiple sclerosis. Gait Posture 2020;76:122-7.
43. Tolbert D. Trunk Stability and Postural Stability in People with Multiple Sclerosis. South Dakota State University; 2018.
44. Gates DH, Dingwell JB. The effects of muscle fatigue and movement height on movement stability and variability. Exp Brain Res 2011;209:525-36.
45. Kellis E, Galanis N, Kofotolis N, Hatzi A. Effects of hip flexion angle on surface electromyographic activity of the biceps femoris and semitendinosus during isokinetic knee flexion. Muscles Ligaments Tendons J 2017;7:286-92.
46. Farrell JW 3rd, Motl RW, Learmonth YC, Pilutti LA. Persons with multiple sclerosis exhibit strength asymmetries in both upper and lower extremities. Physiotherapy 2021;111:83-91.
47. Potvin JR, Fuglevand AJ. A motor unit-based model of muscle fatigue. PLoS Comput Biol 2017;13:e1005581.
48. Dutta R, Trapp BD. Mechanisms of neuronal dysfunction and degeneration in multiple sclerosis. Prog Neurobiol 2011;93:1-12.
49. Smith KJ, McDonald WI. Mechanisms of symptom production. In: Blue Books of Practical Neurology. Vol. 27, Ch. 5. Oxford: Elsevier Inc., 2003. p. 59-74.