ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.surgicalneurologyint.com

Surgical Neurology International
Editor-in-Chief: Nancy E. Epstein, MD, NYU Winthrop Hospital, Mineola, NY, USA.
SNI: Inflammation
Editor
Russell Blaylock, MD
Advanced Nutritional Concepts and Theoretical Neurosciences, Flowood, MS, USA

SNI
Open Access

Original Article

Impact of delayed treatment on exacerbations of multiple sclerosis among Puerto Rican patients

Sara Zarei[1], Irvin Maldonado[1], Laura Franqui-Dominguez[1], Cristina Rubi[2], Yanibel Tapia Rosa[1], Cristina Diaz-Marty[1], Guadalupe Coronado[1], Marimer C. Rivera Nieves[1], Golnoush Akhlaghipour[3], Angel Chinea[2]

[1]Department of Neurology, San Juan Bautista School of Medicine, Caguas, Puerto Rico, [2]Caribbean Neurological Center, Guaynabo, [3]Department of Neurology, University of California, Los Angeles, California, USA.

E-mail: *Sara Zarei: szarei@sanjuanbautista.edu; Irvin Maldonado: imaldonado@sanjuanbautista.edu; Laura Franqui-Dominguez: lfranqui@sanjuanbautista.edu; Cristina Rubi: cristi_rubi2010@hotmail.com; Yanibel Tapia Rosa: ytapia@sanjuanbautista.edu; Cristina Diaz-Marty: cristinadm@sanjuanbautista.edu; Guadalupe Coronado: gcoronado@sanjuanbautista.edu; Marimer C. Rivera Nieves: marimercrn@sanjuanbautista.edu; Golnoush Akhlaghipour: golnoush.akhlaghi@gmail.com; Angel Chinea: achinea@me.com

***Corresponding author:**
Sara Zarei, MD, PhD,
San Juan Bautista School of Medicine, Caguas, Puerto Rico, USA.

szarei@sanjuanbautista.edu

Received : 24 July 19
Accepted : 26 August 19
Published : 11 October 19

DOI
10.25259/SNI_252_2019

Quick Response Code:

ABSTRACT

Background: There are limited data on multiple sclerosis (MS) patients in underserved groups, including Puerto Rico. In this study, we analyzed the characteristic of MS symptoms and number of relapses in Puerto Rican patients. We then compare these characteristics with MS patients from the US. The number of MS relapses is highly correlated with the treatment onset and adherence. Patients in Puerto Rico have been experiencing lengthy treatment delay. We will discuss the possible causes of such delay and its impact on MS prognosis.

Methods: This retrospective cohort study consisted of the evaluation of 325 medical records from MS patients attending the Caribbean Neurological Center from 2014 to 2019. We gathered symptoms and comorbidities data as binary objects. The treatment delay was calculated based on the mean value of days between diagnosis and treatment onset for these groups of patients.

Results: We found that on average, the treatment delay for MS patients in Puerto Rico (PR) to receive their medication was 120 days. The most common MS subtype was relapsing-remitting 72.8%, with a mean of 1.684 relapses per year. Initial symptoms were sensory 54%, visual 33.1%, motor 28.8%, coordination 23.2%, fatigue 9.7%, memory 7.3%, depression 6.5%, urinary 4.9%, gastrointestinal 2.4%, and sexual dysfunction 1.6%. The most common comorbidities were hypertension 18.4%, asthma 13.6%, and thyroid disease 12.8%. When we compared the comorbidities between the two populations, immune thrombocytopenia had the highest percent change with the value of almost 200% (0.001% of US patient vs. 0.8% of Puerto Rican MS patients).

Conclusion: Patients from Puerto Rico had a 33% higher relapse rate compared to the one reported for MS patients in the US. This higher rate may be related to the long delay in receiving their medications. They also had a higher rate of complex comorbidities such as immune thrombocytopenia or thyroid disease. Our findings provide a proof of concept that delay in receiving medications can increase the number of relapses and complex comorbidities among MS patients.

Keywords: Adverse impact of multiple sclerosis treatment delay, Multiple sclerosis comorbidities, Multiple sclerosis symptoms, Multiple sclerosis treatment, Puerto Rican multiple sclerosis patients, Puerto Rico health-care system

INTRODUCTION

Multiple sclerosis (MS) is a chronic, debilitating, and neurodegenerative autoimmune disease that attacks the central nervous system (CNS). The autoimmune reaction causes scarring (sclerosis) of the nerve and interruption of the conduction of nerve impulses from the brain along the spinal cord and to the rest of the body.

MS results in damaging the oligodendrocytes, which cover the axon of CNS neurons and therefore interferes with the neuronal transmission. The degree of demyelination, inflammation, and glial reaction that occurs in MS causes the variation in severity of the symptoms.[82] MS subtypes are a form of classifying the different types of MS, which may differ in disease severity. Standardized clinical stages of MS are divided into four categories, based on clinical criteria, frequency of clinical relapses, time to disease progression, and lesion development on magnetic resonance imaging (MRI). These include relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), primary-progressive MS (PPMS), and clinically isolated syndrome (CIS) which is a subgroup of RRMS.[24]

The onset of symptoms occurs in individuals from 20 to 45 years of age and results in progressive neurological dysfunction. Almost two and a half million people worldwide and more than 700,000 individuals in the United States are living with MS with prevalence rates varying widely in different regions.[53,96]

The incidence and prevalence of MS are greater in higher latitudes farther from the equator and more frequent in females than in males with a ratio of 4:1.[27] In Puerto Rico (PR) the estimated prevalence of MS in 2014 was 42/100,000 and in Central America and the Caribbean ranged from 4.4 to 30/100,000.[18] Studies have shown that there is a growing incidence of MS in PR with an incidence of 6.7/100,000 and a prevalence of 70.6/100,000 (95% confidence interval [CI] 67.4–73.7) in 2016.[19]

MS is incurable which makes the goal of the treatment to slow down the progression and alleviating the symptoms. Disease-modifying medications are used to reduce transient episodes of neurologic disability and limit the accumulation of focal white matter lesions on MRI.[46] The treatment of MS depends on each individual patient's clinical presentation.[79] Most of the treatments such as disease-modifying therapies (DMT) focus on reducing the relapse of the disease and are commonly used in patients with RRMS or SPMS.[79] At present, there are around 12 DMTs approved by FDA for the treatment of MS due to the progressive understanding of the pathophysiology of the disease.[16] DMTs are associated with a lower long-term risk of MS progression.[15,49] Studies have shown that MS patients currently have a longer life expectancy due to earlier treatment management and consequently slower or even prevention of brain damage. MS leads to progressive brain atrophy; therefore, clinicians believe that treatment must be given before MS leads to irreversible brain damage.[16]

Corticosteroids have been also one of the most reliable first choices of treatment for several years, they have been useful in both accelerating recovery, and shortening the duration of relapse.[79] Decreasing the frequency and severity is the goal of treatment in some MS patients such as those diagnosed with RRMS. In the case of SPMS the choice of treatment is to avoid continuous deterioration of the patient's health status. A European study found that there is a delay in neurological deterioration in SPMS patients who use interferon beta-1b. They observed reductions in number of steroid courses needed, number of admissions to the hospital, and time to develop into a wheelchair-bound.[78]

Adherence is one of the most important factors to further increase the probability of treatment success in MS patients. A study from Al-Sabbagh *et al*. observed that patients with 90 or more days of gaps between therapies showed around two-fold greater risk of a severe relapse of MS.[2] By ensuring treatment adherence, patients receive the maximum benefit and therefore a better outcome from these medications. Treatment adherence to prescribed regimens for MS also leads to prevention of health cost inflation and a decreased risk of treatment failure.[76]

Some of the important factors that could cause the delay in the process of providing MS patients with appropriate therapy include insurance companies' authorization process, availability of the drugs in local pharmacies, and lack of knowledge about MS disease among the health administration clerks. One of the most prevailing obstacles for both neurologists and MS patients in Puerto Rico is the long delay in receiving the medications. This could be also due to a lack of medical insurance coverage, making this one of the most important determinant factors that impact the overall health of patients with MS. This prolongation to start treatment leads to more exacerbations of their symptoms and an irreversible shift to a higher stage of the disease.[55,100]

Puerto Rico's Government Health Care and Plans are constantly being reformed due to the economic situation in the Island, and this creates enormous issues when citizens seek medical assistance and treatment. In 2014, Puerto Rico had the highest health insurance coverage rate of about 94% while in the US mainland coverage at that time was about 88%. Even though a high percentage of Puerto Ricans had health insurance coverage, only 36% received insurance through private providers; the rest had publicly funded insurance.[84] Publicly funded insurance plans usually cause certain limitations and delay to immediate health assistance for patients with chronic illnesses. This is due to the need for primary physician referrals for obtaining special studies and

visits to specialists. Insurances in the Island have a managed care model that has to approve certain services or specialist referrals. Submitting these type of requests by primary physicians take time to be processed, and it may end up being declined with no explanation to the patient, leaving patients without the medical attention they need.[77]

Once patients are diagnosed and approved to start the treatment, many other issues may arise. Many insurance companies will deny patients' prescribed DMT due to insurance company preferring a more affordable drug than the one prescribed by the physician.[11] Having a specific prescription denied to a patient elongates the process of starting treatment since this will begin a process of appeal, which may take days to months. Another factor that may delay treatment initiation is the availability of the drug or the time it takes to receive the medication in the Island due to its geographic location. Unfortunately, there has not been any study regarding the cause of such delays in more details.

In addition to the variation of quality of treatment, multiple studies show variations in prevalence, comorbidities, clinical, and demographic features of MS among different populations. Like many other autoimmune diseases, race and ethnicity are known as important factors on disease phenotype, clinical outcomes, and associated comorbidities.[99] For years the comorbidities of MS patients have been under study, some comorbidities such as diabetes and hypertension have been found in similar prevalence in the general population in comparison with MS patients.[65] It has also been found that comorbidities are associated with socioeconomic status in MS patients and they tend to have an average of 1.2 more chronic conditions than the rest of the population.[14,54] These diseases impact the health-related quality of life of the MS patients and aggressively treating them could potentially improve it.[59] In a study performed by North American Research Committee on Multiple Sclerosis (NARCOMS) in 2006, 77.1% of the MS patients reported having at least one comorbidity.[54] The pre-existence of comorbidities within MS patients has been attributed to delay of MS diagnosis. In other words, comorbidities can mask MS by physicians attributing common MS symptoms to other existing conditions.

There is limited data about MS patients in underserved groups, including Puerto Rico. In this study, we analyzed Puerto Rican MS patient's specific symptoms based on data provided by the Caribbean Neurological Center. Furthermore, we evaluated the exacerbation of their symptoms as the result of the delayed time in receiving their medications. Finally, we analyzed the wide variety of comorbidities associated with Puerto Rican MS patients. Our objective was to provide significant findings that will result in an earlier diagnosis as well as an immediate treatment option for MS patients. This study can serve as a stepping stone to adopt new methods of how to improve the quality of MS patients' life by the early diagnosis as well as treatment.

METHODS

This retrospective cohort study focused on MS patients from Puerto Rico. The study sample consisted of 325 MS patients that visited the Caribbean Neurological Center when they were initially diagnosed with MS any time from the years 2014 to 2019. The electronic medical record contains demographic information, patient's vital signs, medical history, family history, social history, recent and past prescribed medication, Expanded Disability Status Scale (EDSS), initial MS symptoms, number of relapses, Vitamin D3 status, MS subtypes, and diagnostic test results. Patient written consent was not required for this study since the datasets were without personal identifiers. The studied data did not include any identifiable information such as names, addresses, date of birth, social security numbers, driver's license numbers, and telephone numbers. The study protocol was approved by the San Juan Bautista School of Medicine Institutional Review Board, Caguas, Puerto Rico.

The raw data were analyzed using R software. For all associated symptoms or comorbidities, data were collected as binary objects, "1" for the existence of a disease or symptom and "0" when it was not present in a patient. To obtain the amount of treatment delay, we calculated the average number of days between the time patients was diagnosed with MS and the time patient obtained the prescribed medications for all MS patients in our dataset. We also performed a comprehensive literature search on characteristics of MS patients from the US and created a table that compares their disease characteristics and comorbidities with MS patients in PR.

For MS patients from the US, we used multiple resources/references in our tables to find the corresponding characteristics and comorbidities. However, for the graphs, we used the most recent study to compare the two populations.

RESULTS

Our sample of 325 MS patients from the Caribbean Neurological Center database consisted of 75.9% females and 24.1% males. The average age at diagnosis among this population was 39 years ranging from a minimum of 15 to 64 years. We found that on average, it takes 120 days for MS patients in PR to receive their medication after they are diagnosed with MS.

We also evaluated common factors previously used for studying MS. These include MS subtypes, initial symptoms, family history of MS, Vitamin D deficiency; gait disturbance,

smoking, working, and disability status of MS patients in PR. Table 1 and Figure 1 present a comparison of our findings with MS patients from the US.

MS subtypes and initial symptoms

The most common MS subtype among patients in PR is RR 72.8%, followed by CIS MS with 14.8%, secondary progressive with 11.1%, and primary progressive with 1.2%. The number of relapses among our MS patients ranged from 0 to 7 relapses per year; with a mean of 1.684/year and a median of 1 annually.

The first symptoms presented by our group of MS patients were predominantly sensory, visual and motor symptoms. The distribution of these initial symptoms was as follows: sensory 54%, visual 33.1%, motor 28.8%, coordination 23.2%, fatigue 9.7%, memory 7.3%, depression 6.5%, urinary 4.9%, gastrointestinal 2.4%, and sexual dysfunction 1.6%, as illustrated in Figure 2.

Family history of MS

One of the predisposing factors for MS is the existence of a history of MS among family members. Our study showed that 11.3% of our patients had a family history of MS. This includes either parents or siblings.

Vitamin D levels

Vitamin D deficiency (<30 ng/mL) was seen in 71.7% of PR MS patients. Previous studies also have demonstrated that Puerto Ricans have low Vitamin D levels, despite the high sun exposure.[80]

Gait, balance, and walking aid use

Use of a walking aid can be an indication of the amount of disability present in an MS patient. In fact, the use of walking assistance helps to determine the EDSS in these patients. In this group of MS patients, we found that 19.5% were using a walking aid, while 4.4% had previously used walker assistance. Therefore, 76.1% of our sample of PR MS patients can be considered fully ambulatory.

Smoking

Our study demonstrated that only 8.8% of patients are current smokers and 12.3% have a previous smoking history. Hence, a total of only 21.1% of PR patients were smokers sometime in their lifetime.

Working and disability status of patients

Our analysis demonstrates that 44.3% of Puerto Rican MS patients are working, 23.7% are disabled, and 4.4% are retired. This suggests that there is a large portion of the population that is not working (55.7%) and not receiving any benefits.

Comorbidities

An analysis of comorbidities among our population of MS patients in PR showed that the most common condition is

Table 1: Comparison of multiple sclerosis characteristics between patients from US and Puerto Rico.

	US Mainland	Puerto Rico
Female versus Male ratio	Percent: 76.5% versus 23%[16] 78.3% versus 21.7%[61] Ratio: 3.60:1.0[60] Incidence F: M 3.6:2.0[3]	Percent: 75.9% versus 24.1% Ratio: 2.7:1 F: M Incidence F: M 99.8/100,000 versus 37.1/100,000[20]
MS subtypes %	Relapsing-remitting: 54.6% Clinically isolated syndrome: 0.4% Secondary progressive: 21% Primary Progressive: 9.1%[81]	Relapsing-remitting: 72.8% Clinically isolated syndrome: 14.8% Secondary progressive: 11.1% Primary progressive: 1.2%
Vitamine D Levels Normal versus Not normal	58.4% versus 41.6%[77]	28.3% versus 71.7%
Walking aid (Ratio: Yes: No)	16:84[34] Ambulatory aids: 5% No ambulatory aid: 86% Cannot walk: 8.9%[16]	No aid: 76.1% Aid: 19.5% Previous use: 4.4%
Family history of MS	12.6%[36]	11.3%
Smoker	53.4% smoker[62] 54.2% smoker[56]	21.1% smoker (8.8% current smoker and 12.3% past use)
Employed versus not working	43.2% versus 56.8%[93]	44.3% versus 55.7%
Disability	Disability: 48%[93] Disability: 37.2%[92]	Disability: 23.7%

MS: Multiple sclerosis

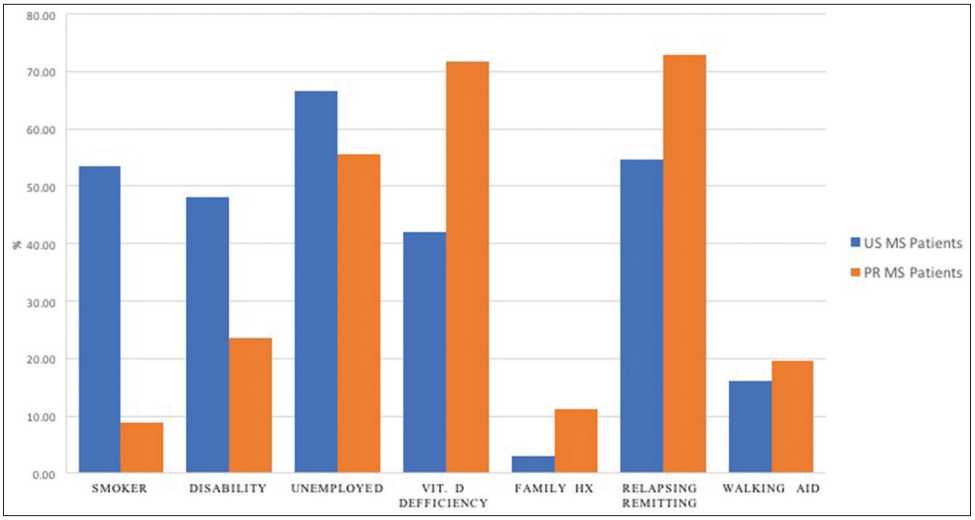

Figure 1: Comparing the characteristics of Multiple Sclerosis between patients from US and Puerto Rico..

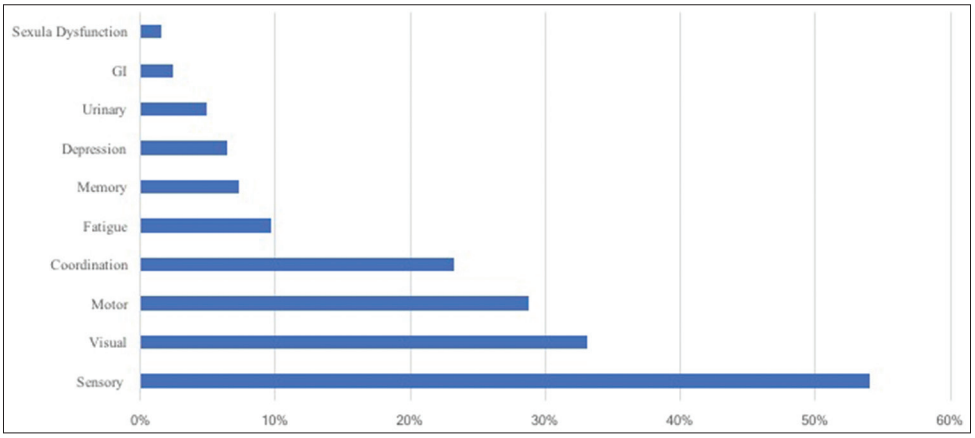

Figure 2: Initial Symptoms of Puerto Rican MS patients.

hypertension (18.4%). Other conditions observed that were above 10% were: asthma (13.6%), thyroid disease (12.8%), and migraine headaches (12%). Table 2 and Figure 3 show the comparison of common comorbidities between MS patients from Puerto Rico and the US. To illustrate the differences when comparing the comorbidities between the two populations, we calculated the percent change for each comorbidity. As shown in Figure 3, immune thrombocytopenia had the highest percent change with the value of almost 200%, given the fact, only 0.001% of the US patient had this disease versus 0.8% (n = 26) of Puerto Rican MS patients.

DISCUSSION

In this study, we found a distribution of 75.9% females and 24.1% males among the 325 MS patients evaluated from the Caribbean Neurological Center database. These results are consonant with the fact that MS is more prevalent in females than males. Our ratio, 3/1, differs slightly from the one reported in several studies, ranging approximately 4:1.[22,47] The range for age of diagnosis was from 14 to 65 years, with a mean value of 39 years. Chinea *et al*. reported that in Puerto Rico the range of ages of MS in both men and women for the onset of symptoms is 20–50 years; meanwhile, the range of ages for the diagnosis is 35–54 years.[17] These indicate that there were extreme values in our population.

When looking for MS subtypes percent in the United States population, RRMS had the highest percent, with 54.6% in a study that reported five different subtypes.[83] Other studies undertaken in the US with only three subtypes, showed a higher percent for RRMS with 94.8, 5.2 for SPMS, and 0 for PPMS.[32] Based on our findings, the most common type of MS among PR patients was RR, which is similar to the most common type among the US patients. However, the second most common MS subtype in the PR population is CIS. This finding is surprising since CIS MS tends to evolve to RR MS.

Table 2: Comparison of common comorbidities between MS patients from Puerto Rico and US.

Comorbidities	MS patients in USA	MS patients in PR
Diabetes	4.1% (CI 2.8–5.4)[57] 5–6.1%[58,63]	6.4%
Thyroid	4.6%[55]	12.8%
Allergies	4.9%[82]	3.2%
High cholesterol	37%[58]	8.0%
High blood pressure	8.0%[55] 16.7%[57] 30.1%[58,63]	18.4%
Migraine	42.5%[32]	12.0%
Asthma	5.3%–9%*[10] Lung disease: 13%[63]	13.6%
Immune diseases	All together: 8.7%[55] Arthritis: 18% (CI 15.4–20.5)[57] 16%[63]	All together: 1.6%
Immune thrombocytopenia	0.001%*[10]	0.8%
Osteoporosis	17.5%[60]	1.6%
Psychiatric	8.1% of Patients reported symptoms of depression: 1.4% Caucasian 3.2% Latino 3.5% African American[91] Depression types: No depression: 29.4% Minimal-mild: 42.4% Moderate-severe: 13.2%[81]	6.4%

MS: Multiple sclerosis, CI: Confidence interval, *9.0%

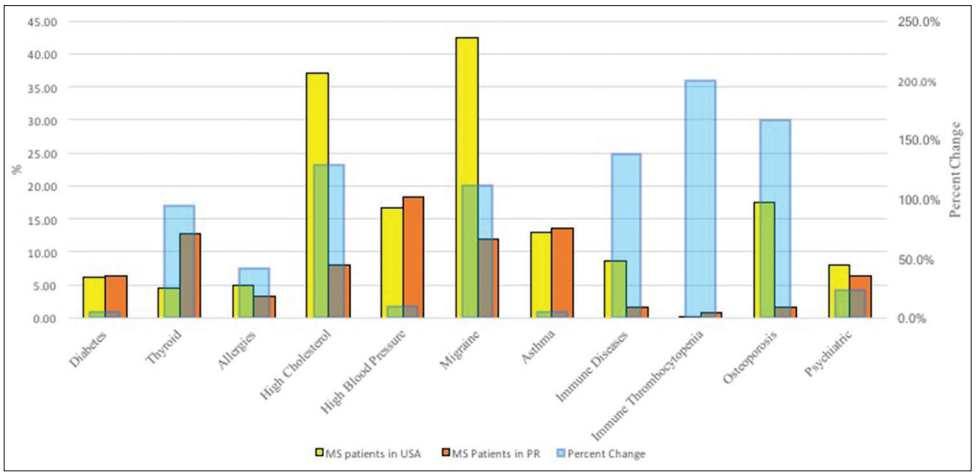

Figure 3: Comparison of common comorbidities between MS patients from Puerto Rico and US.

The discrepancy might be attributed to the fact that the data were collected at the moment of diagnosis. RR is characterized by a surge of symptoms followed by recuperation and stability. In both the US and PR, it is shown that the more aggressive forms of MS are less common among these population.

In terms of the first symptoms of MS that our patients presented, sensory, visual, and motor symptoms were predominant. Stoppe *et al*. evaluated the symptoms their patients presented in relapses, and they are similar to the initial symptoms that our patients presented. They reported: sensory 42%, motor 29.4%, and visual 24.4% in all documented relapses.[91] However, it is important to note that Stoppe *et al*. results were from relapses and ours were the initial presenting symptoms.

The initial symptoms of our MS patients were mostly a combination of the typical common symptoms such as optic,

sensory, motor, brainstem, and cerebellar signs.[40] However, there were four females that presented only memory problem along with fatigue. These type of rare MS initial symptoms makes the early diagnosis of MS rather complicated. Hence, it is crucial not to disregard MS even when patient has rare combination of symptoms.

MS has not been shown to be a genetic disease, though it is common to see multiple family members suffering from MS. In fact, it has been reported that there is a 15%–20% risk of having a family member also affected with the disease.[25] The prevalence of familial MS was estimated at 12.6% worldwide.[34] In Puerto Rico, 11.3% of MS patients have at least one family member with MS. Moreover, the predisposition of, or resistance to MS, as well as the course and severity of the disease in Puerto Rican patients has been associated with specific HLA allele types. For example, HLA-DQB1*04 is thought to be protective while HLA-DRB1*01 was found to be the most represented allele in MS patients and related to a more benign course of the disease. Although a strong association has been reported between MS and genetic and environmental factors, no causality or correlation to the number of relapses has been established yet.[67]

Analysis of Vitamin D levels is important in MS patients because it has been demonstrated to be a risk factor for developing MS.[70] Higher Vitamin D levels have been associated with lower risk of MS and lower MS activity has been reported on MRI in patients with high levels of Vitamin D.[10] Furthermore, a lower rate of progression of MS has been seen in patients with higher 25(OH)D.[6] The low levels of Vitamin D among Puerto Rican have been suggested to be a result of high sunscreen use and the darker skin color, which is known to absorb less Vitamin D.[18,20,48,89] Low levels of Vitamin D are commonly found among MS patients worldwide, and US and PR both share this characteristic. Although a higher percentage of Vitamin D deficiency was found initially, in the lab work reviewed on the first visit of PR MS patients (71.7%) compared to US patients, it is important to note that 100% of these patients underwent Vitamin D supplement therapy until reaching normal to higher Vitamin D levels. Vitamin D supplements are a common over-the-counter product available in all retail pharmacies in Puerto Rico and can be acquired without a prescription or insurance coverage. Furthermore, studies have shown popular use of Vitamin D supplements specifically in Puerto Rico's elderly female population. The cultural acceptance of vitamin supplementation could increase compliance of treatment.[74] Our study showed that PR MS patients had greater number of relapses when compared to the US MS and these relapses occurred despite the fact that patients where maintaining a normal level of Vitamin D.

Moreover, in terms of walking aid use in our study, we found that 76.1% never used one while 19.5% were using assistance and 4.4% used in the past. Around 75% of MS patients will experience gait and balance problems throughout their lives.[45,71] Older age, female, active spasticity and fatigue, cognitive impairment, and a greater ambulatory disability are characteristics associated with the use of assistive devices.[58] Our results showed almost 24% of Puerto Rican MS patients had used walking aid. Studies of reported data in NARCOMS found that 52.2% of responders had a fall in the past 6 months.[30] Therefore, it is common that many of MS patients would require a walking aid. Another study conducted in the US reported that 16% of MS patients, with higher percentage of female (F:M-71:21), used a walking aid.[32] Other study using self-reported information by patients in the NARCOMS found that 16.9% Caucasian (C), 14.9% Latinos (L), and 16.2% African American (AA) had occasional use of a cane or unilateral support and compared it with 8.2%, 7.1%, and 10.1%, respectively, that use bilateral support due to severe gait disability.[13]

These numbers (in both PR and US) are very low in comparison with the percentage in Australia (48%) and United Kingdom (74%) reported in the same study.[32] It will be interesting in the future to investigate why is the mobility aid use so low among patients from US and PR and if it is related to social stigmatization. Furthermore, efforts have been made to assess the safety of the patient while using ambulatory aid due to an increased risk of falling associated with walking aid. This is mostly due to the fact that some patients did not receive adequate information about proper use of walking aid and fall prevention strategies.[26]

Lifestyle of the patients affects the course of the diseases, and smoking is an important variable to MS progression. Our study demonstrated that the smoking status of our subjects was 78.9% never smoke, 8.8% current smokers, and 12.3% smoked in the past. Hence, a total of 21.1% of our MS patients were cigarette smokers. This is much lower than reported in the US (53.4%).[56] It has been recently found that men who smoke have a higher risk of MS than women.[7] According to Chinea *et al*., 26.4% of Puerto Rican MS patients had a current or previous history of smoking, which was very close to our findings.[18] Smoking puts individuals at a higher risk of developing MS as well as causing progression of the disease among MS patients.[23] In a study conducted by Hedström *et al*., they demonstrated that people who smoke or is exposed to second-hand smoke have increased risk of MS due to both smoking influence on HLA genotype and the pro-inflammatory effects that the irritants of tobacco have in lungs.[35]

Marrie *et al*. reported smoking increases the risk of developing autoimmune comorbidities in MS patients (hazard ratio: 1.23; 95% CI: 1.08–1.41).[61] Another study suggested that smoking should be even evaluated as a

comorbidity in MS patients since they were more prompt to be smokers than the general population.[62] Cessation of smoking also plays an important role in the progression of the disease. It has been reported that there is significant and time-dependent diminution in the risk of disability on those patients that stopped smoking.[92]

MS can progress as a severely debilitating disease that affects the CNS causing symptoms such as fatigue, pain in multiple sites, and impairment of upper and lower limb function, among others.[3,4,58] As disease progresses, it impairs physical and cognitive functions.[87] Therefore, it is common to see many MS patients who are disabled or otherwise unemployed. In terms of working status among our patients, 44.3% were worked, 23.7% were disabled, and 4.4% were retired. A recent study by Smith *et al*. showed that 20% of MS patients in the US were working less hours, 42% were not working, and the remaining 38% were working depending on their different stages of MS and clinical presentations.[90] This is important since a great number of MS patients are in early (productive) ages. Hadjigeorgiou *et al*. reported that 58.89% of MS patients who are employed, had been absent from work due to problems with health services.[33] This means that the disease is going to carry an extra burden to the economy by taking away years of productivity that MS patients would have contributed.

Studies have shown that many patients live constantly exiting and re-entering to the workforce depending on their disease progression and the overall impact on their body functionality.[41] Several studies reported that both physical limitation and cognitive impairment in MS patients can affect their future in the work force and will have an effect on work opportunities.[69,81] A qualitative study in Malaysia showed that under a lot of work-related stress or pressure, the MS relapse will come faster.[95] This opens the discussion for a revision on which type of work and how many hours MS patients should be working.

A study that grouped responses from Canadian and United States patients reported that employment was higher in RRMS patients (43.1%) in comparison with PPMS patients (18.1%).[87] The same study by Amber Salter *et al*. reported that 48.5% of the responders answered that were receiving disability benefits.[87] Campell *et al*. reported a nonadjustable mean of unemployment among MS patients of 60%, higher than the mean of 27% among nonMS population.[14]

Based on our results, only 44.3% of PR MS patients were employed. Thus, we have a much lower percentage of employment among this population compared with MS patients from the US. The low employment status of the PR patients could be attributed to the Islands high unemployment rate since it is shown that only 23.7% of patients are disabled while in the US, the number is a much higher 48% disability rate.[87]

It is important to acknowledge that the patients were classified as disabled if before the interview they had been granted social security benefits. Approximately 70% of the Puerto Rican applicants will be denied each year, and the process may take from 4 months up to 2 years depending on the number of denials and appeals.[37] This could be a primary reason for the patients not applying for social security disability benefits and thus not being classified as disabled when interviewed.

The employment ratio by race in the US is as follows: C 47.5%, L 46.9%, and AA with 38.6%.[41] Another study that discusses the major concerns of Latinos with MS in the US reported that 40–46% were dissatisfied with their jobs since they had difficulties requesting job accommodations. For instant they had problem with having the accommodation in a short period of time, requesting for assistive technology for their jobs and requesting changes in their tasks without fear of losing their job.[85] This difficult process of requesting accommodation and changing their responsibilities at their job could have a negative impact on keeping their current position. Hence, health professional has an important role in guiding and helping MS patients to remain active at their work.[72]

Comorbidities play an important role in the progression of MS. As the patient grows older, the more comorbidity he/she will have. Diseases such as hypertension, diabetes, and hyperlipidemia are among the most common.[62]

Comparing our results with the MS comorbidities of the US population were a bit challenging since the US data stems from different sources and include different races and ethnic groups. However, as shown in Table 2, it is evident that metabolic disease, such as diabetes, thyroid disease, and hyperlipidemia, is common among both groups and also seen in high percentages among both groups are hypertension. These diseases are common among the general population in both US and PR.

Diabetes

Our result indicates that 6.4% of our MS patients had diabetes. This was slightly higher from what has been reported among MS patients in the US. In 2014 according to the Behavior and Risk Factor Surveillance System, 15.7% of Puerto Rican population were diabetic while the corresponding percentage in US was only 10.1% at that time. This shows in general, Puerto Rican has a higher risk of diabetes in comparison to US.[88]

In MS patients that suffer from diabetes, the treatment cost can be greater than MS patients with any other comorbidity. This is due to the substantially higher lifetime medical expenditures associated with diabetes and preventing its health complications.[28] Type 1 diabetes is genetically similar to MS and there are studies that suggest both share

etiological components.[38,68,93] In families with a history of autoimmune disease including MS prevalence of diabetes was found to be 0.19%–0.3%.[9] In the general population of MS patients a range of 4.1%–6.1% have been found to have diabetes mellitus.[52,64,54] It has been shown that both diabetes and hypertension can have direct impact in clinical findings of MS patients. For instant changes in disability, emotional state and walking ability have been associated with these comorbidities.[21]

Hou *et al*. published a study in 2017, demonstrating a significant association between diabetes mellitus type 2 and MS incidence.[36] They reported that MS patients with diabetes mellitus type 2 had higher prevalence of allergies, thyroid disease, dyslipidemia, depression, and anxiety, among others; and they had more overall visits to their physician.[36]

Thyroid disorders

Our result shows that 12.8% of the Puerto Rican MS patients studied had thyroid disease. On the other hand, only 4.6% of MS patients in the US were found with thyroid disorders.[60] In a study done by Mattei *et al*., 17.7% of Puerto Ricans were found to have thyroid conditions independent of MS diagnosis, based on self-reported medically-diagnosed conditions.[66] This higher rate of thyroid disease among MS patients in Puerto Rico could be due to worsening of their MS condition associated with delay in onset of MS treatment. As we discussed earlier, the more MS progress, the more patient is susceptible to other comorbidities including the thyroid-related disease.

Thyroiditis among other autoimmune diseases has been found to influence changes on the brain in MS patients.[51] Good screening and treatment of thyroid diseases are vital in MS patients to avoid progression or relapses of disease.

Hyperlipidemia

High cholesterol was found in 37% of the US patients that reported comorbidities to the NARCOMS.[54,64] Only 8% of Puerto Rican MS patient presented with hyperlipidemia. Studies have found an association between higher LDL-C ($P = 0.006$) and total cholesterol (TC) ($P = 0.001$) with an increase of T2 lesions over the past of 2 years in patients with demyelinating diseases.[64,97] Therefore, it is important to asses for MS patients lipid profiles due to the association of high levels of cholesterol and inflammatory MRI activity.[97]

Hypertension

Multiple studies have reported that 8%–30.1% of MS patients in the US are suffering from hypertension.[52,60,64] In comparison with these percentages, 18.4% of Puerto Rico MS patients were found to have high blood pressure. Hence, both populations seem to have hypertension as the most frequent comorbidity among their MS patients.

Migraines/headaches

In a meta-analysis performed by Foley *et al*., the prevalence of pain due to headache was found in 42.5% (95% CI 33.2%–52.1%) of the patients suffering from all MS subtypes.[31]

Among our patients, 12% presented with migraine headache. This is lower compared to MS patient from the US. This discrepancy could be explained by the fact that the prevalence of migraine headache is lower among PR general population compared to the US. According to a study by Miranda *et al*., prevalence of migraine headache among Puerto Rican was 13%. Hence, MS patients carry similar prevalence rate of migraine headache as the general population in PR.

Asthma/lung disease

Pulmonary diseases are common in MS patients. A meta-analysis from Europe and North America found a range of 0.5%–25.0% for asthma and a 0.62%–2.9% range for COPD in MS patients.[63] Studies performed in the US have found that a range of 5.3%–9% of the MS patients suffer from asthma and 13% suffer from any types of pulmonary disease.[9] Our result shows that 13.6% of Puerto Rican MS patients had asthma/pulmonary disease which is very similar to those from the US.

Immune diseases

Autoimmune diseases were reported in 8.7% of the patients who responded to the 2006 questionnaire by NARCOMS in the US.[60] The percent of patients suffering from arthritis has been found to have a range from 16% to 18% in the US. Other autoimmune diseases, such as Sjogren's Syndrome, have also been found among MS patients with a very low prevalence.[5] In a study that evaluated the prevalence of autoimmune diseases in families with numerous members with MS as first-degree relative, 64% of the families reported at least one autoimmune disease.[9] Almost 2% of our patients had autoimmune disease. According to the study conducted by Barbour *et al*., Puerto Ricans are found to have the highest age-adjusted prevalence of arthritis (21.8%) among other special racial and ethnics group.[8] This indicates that our patient may not have been diagnosed with an autoimmune disease at the time of their MS diagnosis.

Immune thrombocytopenia

Almost 1% of our patients presented with immune thrombocytopenia. This was higher than US patients, with only 0.001%. Marrie *et al*. reported that Alemtuzumab, one of the medications that patients are using to treat MS, can

cause immune thrombocytopenia.[62] This raises the question of whether this medication is more common in PR compared to the US due to insurance companies' policy or preference for certain medication. Other possible explanation for this phenomenon is increased incidence of Zika virus infection in Puerto Rico that causes immune thrombocytopenia.[94] However, more research is needed to discover the underlying reason for immune thrombocytopenia among MS patients in Puerto Rico.

Osteoporosis

In 2007, 27.2% of the MS population in North America reported low bone mass or osteoporosis.[57] Our study indicated only 1.6% of our patients had osteoporosis compared to the US with 17.5%. A possible explanation is that osteoporosis is more common among US general population hence higher percentage of MS patients in the US tends to have osteoporosis in comparison with PR patients. In a study conducted by Wright *et al*., using the national data they estimated that 43.4 millions of US older adults had low bone mass, and osteoporosis and most of them were non-Hispanic white women.[98]

Psychiatric

Psychiatric disorders are common in patients suffering from MS around the world.[75] Major depression is the most common psychiatric disorder among MS patient, and it is an important element for the morbidity, quality of life, mortality, and the progression of disease.[75] Our result showed 6.4% of our patients suffered from depression. Buchanan *et al*. conducted a study in the US found that a total of 8.1% of the MS patients were diagnosed with depression.[13] They reported a higher percent of African Americans (3.5%) followed by Latino patients (3.2%) and Caucasian (1.4%).[13] Other studies have reported 8.4% of the MS patients interviewed, had mental disorders comorbidities.[60] In studies asking for the presence of depressive symptoms in the past 12 months, 40% of the MS patients answer with positive findings.[12,60] Marrie *et al*. pointed out that depression and anxiety disorders can be classified as comorbidity as well as a complication of MS.[62] Hence, screening MS patients for depression and anxiety must be a routine process during their physician visit time.

As we mentioned earlier, on average, it takes 120 days for MS patients in PR to receive their medication after they are diagnosed with MS. Such delay in receiving medications can cause more relapses and complex comorbidities among Puerto Rican MS patients.

Consequences of delay in treatment

Our findings showed that the number of RRMS is higher among PR MS patients in comparison with patients from the US. In terms of relapses, the values from our study ranged from 0 to 7 relapses per year; with a mean of 1.684 per year and a median of 1 annually. On the other hand, in a study conducted by Olek, the frequency of relapses among MS patients in the US was 1.27/year.[73] Hence, patients from Puerto Rico had 33% higher relapse rate, in part due to the long delay in receiving their medication.

The number of relapses and neuronal disability progression in patients that are more adherent to their treatment has been reported by previous studies to be relatively lower in comparison with the patient that is not receiving treatment for any reason.[50] Moreover, there is evidence that patients who are less adherent with treatment had more inpatient (hospitalizations), emergency department visits, and more severe relapses, which are important determinants of disease prognosis.[50]

The benefits of early treatment of MS have been proven in multiple studies and have shown to decrease the frequency of relapses and slowing progression of the disease-related disability.[43] The consequences of delay in treatment have not been reported to such extent in comparison to the benefits of early treatment for clinically diagnosed MS patients. In 2007, Kappos and Freedman started a progressive study in which they randomly placed MS patients into two different treatment groups. One group received Interferon B-1b and another group had placebo for 2 years. After 2 years, all patients received treatment and were followed up for 3 more years. After 3 years 51% of the patients that had delayed treatment developed clinically definite MS versus 37% of the patients that started early treatment.[42] The study found that the delay in treatment even by only one prior event had substantial disability impact in MS patients due to subclinical neuronal damage that persisted.[29,42] When comparing patients that started treatment early versus those with delayed treatment, it showed no significant difference in the MS functional composite score. However, there was a significant difference between the two groups in auditory cognitive subtest. Delayed treatment patients were found to have worst results than the early treatment patients.[42] T2 brain lesions were also reduced in patients who were treated earlier with Interferon B-1b compared to those who received placebo.[39,43]

In a study by Adams *et al*., they interviewed elderly Puerto Ricans that are living in the United States mainland. According to their study, the main reason Puerto Rican decided to stay at mainland is due to having easier access to medical services and excess reliance on medications.[1] Puerto Ricans tend to have a lower level of the health-care system and economic status when compared to other Latino groups. Puerto Ricans are also known to have a greater requirement of medications approval process when compared to patients in United States.[1]

Health care contributes to 20% of the Puerto Rican economy, but with the health care crisis it leads to less access to medical care and decreases health-care providers in the Island. Puerto Ricans have to pay Medicare taxes and Social Security; however, in comparison with other 50 states, they receive the least federal funding for health care.[86]

Puerto Rico's medical services were even more disrupted considerably after natural disaster of Hurricane Maria in 2017. The inability to access medications has been the most frequently reported issue. In addition to treatment delays, lack of medical facilities and physicians are among other major issues that have been arising in Puerto Rico.[44] Hence, it is evident that Puerto Ricans MS patients are in desperate need of better access to medications and a relief to their health care crisis.

Limitations

The date of treatment onset was not included in our patients' electronic medical records. Hence, to obtain such information, patients' files had to be accessed manually. Looking through paper medical files takes time specifically when there is large number of patients. We had to go through all the doctors' handwritten notes carefully to find the actual start date of initial treatment. Looking over 325 files became at times dreary which caused this part to take more time than expected. Furthermore, to ensure data were gathered correctly we had more than one person to perform the manual data collection to ensure we have obtained the correct information. If the date of onset of treatment had been in an electronic format, the gathering of such information for this research could have been achieved more efficiently.

CONCLUSION

As previously mentioned, there are limited studies about MS in PR in this critical and growing patient population. However, with this study, we shed light onto the characteristics of the Puerto Rican MS patients and discussed the possible consequences of delay in receiving their medications. Patients from the Caribbean Neurological Center database that participated in this study were demographically similar to those reported in MS-related literature in terms of gender ratio, age of diagnosis, and initial symptoms. The comorbidities that were more predominant in our patients were hypertension, asthma, thyroid disease, and migraines. Immune thrombocytopenia was shown in higher rates among our patients compared to MS patients from the US. Only a few had a family history of MS and most of them reported low Vitamin D3 levels. In terms of MS subtypes, RRMS was first, followed by PRMS, SPMS, and finally by PPMS.

One of the significant issues that Puerto Rican MS patients are currently facing is the delay in receiving their medications. On average, it takes 120 days for MS patients in PR to receive their medication. Consonant with this finding, their average rate of relapse was 33% higher compared to the US. Puerto Rican patients also had a higher rate of complex comorbidities such as immune thrombocytopenia or thyroid disease which could be related to delayed treatment onset.

Insurance companies' authorization process, local pharmacy availability of the drugs and lack of knowledge about MS disease among the administrative clerks all play important factors in delaying the process of providing the MS patients with their medication. This leads to more exacerbations of their symptoms and an irreversible shift to a higher stage of the disease. Given the fact that the majority of MS medications are costly, insurance companies require specific authorizations. Many insurance companies in PR have a lengthy process in issuing authorization for MS medications.

A comprehensive medical and cost analysis need to be performed to provide the health insurance companies and corresponding government agencies with sufficient evidence that delaying these authorization processes will have negative economic consequences.

Hence, our findings serve as a stepping stone for such analysis. To conduct a comprehensive analysis, we would need to collect data from all those patients that had experienced the delay in receiving their medications. Next, we will need to obtain the total aggregated cost as the result of the exacerbations of patients' symptoms. This includes any hospital fees, doctor visit fees, and any additional medication that the patient had to purchase while waiting for the primary treatment to arrive.

Therefore, we could achieve a substantial positive impact on the economy and health-care system by utilizing proper management strategies that lead to less reliance on inpatient care while increasing access to medications at home. Such strategies will reduce the frequency and severity of MS relapses.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Adams WE, Todorova IL, Guzzardo MT, Falcón LM. The problem here is that they want to solve everything with pills: Medication use and identity among mainland puerto ricans. Sociol Health Illn 2015;37:904-19.
2. Al-Sabbagh A, Bennett R, Kozma C, Dickson M, Meletiche D. Medication gaps in disease-modifying drug therapy for

multiple sclerosis are associated with an increased risk of relapse: Findings from a national managed care database. J Neurol 2008;255:79. Available from: https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Medication+gaps+in+disease-modifying+therapy+for+multiple+sclerosis+are+associated+with+an+increased+risk+of+relapse%3A+Findings+from+a+national+managed+care+database&btnG. [Last accessed on 2008 Jun 01].
3. Alschuler KN, Jensen MP, Ehde DM. Defining mild, moderate, and severe pain in persons with multiple sclerosis. Pain Med 2012;13:1358-65.
4. Amato MP, Ponziani G, Rossi F, Liedl CL, Stefanile C, Rossi L, *et al.* Quality of life in multiple sclerosis: The impact of depression, fatigue and disability. Mult Scler 2001;7:340-4.
5. Annunziata P, De Santi L, Di Rezze S, Millefiorini E, Capello E, Mancardi G, *et al.* Clinical features of sjogren's syndrome in patients with multiple sclerosis. Acta Neurol Scand 2011;124:109-14.
6. Ascherio A, Munger KL, White R, Köchert K, Simon KC, Polman CH, *et al.* Vitamin D as an early predictor of multiple sclerosis activity and progression. JAMA Neurol 2014;71:306-14.
7. Ascherio A, Munger KL. Epidemiology of multiple sclerosis: From risk factors to prevention-an update. Semin Neurol 2016;36:103-14.
8. Barbour KE, Helmick CG, Boring M, Brady TJ. Vital signs: Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation United States, 2013-2015. MMWR Morb Mortal Wkly Rep 2017;66:246-53.
9. Barcellos LF, Kamdar BB, Ramsay PP, DeLoa C, Lincoln RR, Caillier S, *et al.* Clustering of autoimmune diseases in families with a high-risk for multiple sclerosis: A descriptive study. Lancet Neurol 2006;5:924-31.
10. Bhargava P, Cassard S, Steele SU, Azevedo C, Pelletier D, Sugar EA, *et al.* The Vitamin D to ameliorate multiple sclerosis (VIDAMS) trial: Study design for a multicenter, randomized, double-blind controlled trial of Vitamin D in multiple sclerosis. Contemp Clin Trials 2014;39:288-93.
11. Bourdette DN, Hartung DM, Whitham RH. Practices of US health insurance companies concerning MS therapies interfere with shared decision-making and harm patients. Neurol Clin Pract 2016;6:177-82.
12. Buchanan RJ, Minden SL, Chakravorty BJ, Hatcher W, Tyry T, Vollmer T, *et al.* A pilot study of young adults with multiple sclerosis: Demographic, disease, treatment, and psychosocial characteristics. Disabil Health J 2010;3:262-70.
13. Buchanan RJ, Zuniga MA, Carrillo-Zuniga G, Chakravorty BJ, Tyry T, Moreau RL, *et al.* Comparisons of latinos, African Americans, and caucasians with multiple sclerosis. Ethn Dis 2010;20:451-7.
14. Campbell JD, Ghushchyan V, Brett McQueen R, Cahoon-Metzger S, Livingston T, Vollmer T, *et al.* Burden of multiple sclerosis on direct, indirect costs and quality of life: National US estimates. Mult Scler Relat Disord 2014;3:227-36.
15. Capra R, Cordioli C, Rasia S, Gallo F, Signori A, Sormani MP, *et al.* Assessing long-term prognosis improvement as a consequence of treatment pattern changes in MS. Mult Scler 2017;23:1757-61.
16. Cerqueira JJ, Compston DAS, Geraldes R, Rosa MM, Schmierer K, Thompson A, *et al.* Time matters in multiple sclerosis: Can early treatment and long-term follow-up ensure everyone benefits from the latest advances in multiple sclerosis? J Neurol Neurosurg Psychiatry 2018;89:844-50.
17. Chinea A, Pérez N, Perez-Canabal A, Rojas F, Torres J, Poser C, *et al.* The Puerto Rico study for the prevalence of multiple sclerosis. Bol Asoc Med P R 2012;104:4-9.
18. Chinea A, Ríos-Bedoya CF, Rubi C, Vicente I, Estades ER, Hernandez-Silvestrini YG, *et al.* Incidence of multiple sclerosis in Puerto Rico, 2014: A population-based study. Neuroepidemiology 2017;48:55-60.
19. Chinea A, Ríos-Bedoya CF, Vicente I, Rubí C, García G, Rivera A, *et al.* Increasing incidence and prevalence of multiple sclerosis in Puerto Rico (2013-2016). Neuroepidemiology 2017;49:106-12.
20. Clemens TL, Adams JS, Henderson SL, Holick MF. Increased skin pigment reduces the capacity of skin to synthesise Vitamin D3. Lancet 1982;1:74-6.
21. Conway DS, Thompson NR, Cohen JA. Influence of hypertension, diabetes, hyperlipidemia, and obstructive lung disease on multiple sclerosis disease course. Mult Scler 2017;23:277-85.
22. Corona T, Román GC. Multiple sclerosis in Latin America. Neuroepidemiology 2006;26:1-3.
23. Di Pauli F, Reindl M, Ehling R, Schautzer F, Gneiss C, Lutterotti A, *et al.* Smoking is a risk factor for early conversion to clinically definite multiple sclerosis. Mult Scler 2008;14:1026-30.
24. Durand M. MS classifications revised. Momentum Mag Natl MS Soc 2016. Available from: http://www.momentummagazineonline.com/ms-classifications-revised. [Last accessed on 2019 Jan 29].
25. Dyment DA, Ebers GC, Sadovnick AD. Genetics of multiple sclerosis. Lancet Neurol 2004;3:104-10.
26. Eitzen A, Finlayson M, Carolan-Laing L, Nacionales AJ, Walker C, O'Connor J, *et al.* The development of an observational screening tool to assess safe, effective and appropriate walking aid use in people with multiple sclerosis. Disabil Rehabil Assist Technol 2017;12:641-6.
27. Epidemiology of MS : National Multiple Sclerosis Society. Available from: https://www.nationalmssociety.org/What-is-MS/Who-Gets-MS. [Last accessed on 2019 Mar 05].
28. Ernstsson O, Gyllensten H, Alexanderson K, Tinghög P, Friberg E, Norlund A, *et al.* Cost of illness of multiple sclerosis a systematic review. PLoS One 2016;11:e159129.
29. Filippi M, Bozzali M, Rovaris M, Gonen O, Kesavadas C, Ghezzi A, *et al.* Evidence for widespread axonal damage at the earliest clinical stage of multiple sclerosis. Brain 2003;126:433-7.
30. Finlayson ML, Peterson EW, Cho CC. Risk factors for falling among people aged 45 to 90 years with multiple sclerosis. Arch Phys Med Rehabil 2006;87:1274-9.
31. Foley PL, Vesterinen HM, Laird BJ, Sena ES, Colvin LA, Chandran S, *et al.* Prevalence and natural history of pain in adults with multiple sclerosis: Systematic review and meta-analysis. Pain 2013;154:632-42.
32. Gunn H, Cameron M, Hoang P, Lord S, Shaw S, Freeman J,

et al. Relationship between physiological and perceived fall risk in people with multiple sclerosis: Implications for assessment and management. Arch Phys Med Rehabil 2018;99:2022-9.
33. Hadjigeorgiou G, Dardiotis E, Tsivgoulis G, Doskas T, Petrou D, Makris N, *et al.* Observational study assessing demographic, economic and clinical factors associated with access and utilization of health care services of patients with multiple sclerosis under treatment with interferon beta-1b (EXTAVIA). PLoS One 2014;9:e113933.
34. Harirchian MH, Fatehi F, Sarraf P, Honarvar NM, Bitarafan S. Worldwide prevalence of familial multiple sclerosis: A systematic review and meta-analysis. Mult Scler Relat Disord 2018;20:43-7.
35. Hedström AK, Katsoulis M, Hössjer O, Bomfim IL, Oturai A, Sondergaard HB, *et al.* The interaction between smoking and HLA genes in multiple sclerosis: Replication and refinement. Eur J Epidemiol 2017;32:909-19.
36. Hou WH, Li CY, Chang HH, Sun Y, Tsai CC. A population-based cohort study suggests an increased risk of multiple sclerosis incidence in patients with Type 2 diabetes mellitus. J Epidemiol 2017;27:235-41.
37. How to Apply for Social Security Disability in Puerto Rico. Available from: https://www.disabilitybenefitscenter.org/state-social-security-disability/puerto-rico. [Last accessed on 2019 Jul 22].
38. International Multiple Sclerosis Genetics Consortium (IMSGC). The expanding genetic overlap between multiple sclerosis and Type I diabetes. Genes Immun 2009;10:11-4.
39. Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, Murray TJ, *et al.* Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS study group. N Engl J Med 2000;343:898-904.
40. Joy JE, Johnston RB Jr., editors. Institute of Medicine (US) Committee on Multiple Sclerosis: Current Status and Strategies for the Future. In: Characteristics and Management of Major Symptoms. Washington, DC: National Academies Press; 2001.
41. Julian LJ, Vella L, Vollmer T, Hadjimichael O, Mohr DC. Employment in multiple sclerosis. Exiting and re-entering the work force. J Neurol 2008;255:1354-60.
42. Kappos L, Freedman MS, Polman CH, Edan G, Hartung HP, Miller DH, *et al.* Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: A 3-year follow-up analysis of the BENEFIT study. Lancet 2007;370:389-97.
43. Kappos L, Polman CH, Freedman MS, Edan G, Hartung HP, Miller DH, *et al.* Treatment with interferon beta-1b delays conversion to clinically definite and mcDonald MS in patients with clinically isolated syndromes. Neurology 2006;67:1242-9.
44. Kishore N, Marqués D, Mahmud A, Kiang MV, Rodriguez I, Fuller A, *et al.* Mortality in Puerto Rico after hurricane maria. N Engl J Med 2018;379:e30.
45. Kister I, Chamot E, Salter AR, Cutter GR, Bacon TE, Herbert J, *et al.* Disability in multiple sclerosis: A reference for patients and clinicians. Neurology 2013;80:1018-24.
46. Ko J, Katic B, Simacek K, Moreton D, Buechler N, Varga S. Disease-modifying Therapy Access Issues and their Impact on Multiple Sclerosis Patients: An Online Mixed Methods Study. Available from: https://www.patientslikeme_posters.s3.amazonaws.com/2016_DiseaseModifyingTherapyAccessIssuesAndTheirImpactOnMSPtsOnlineMixedMethods.pdf. [Last accessed on 2018 Jun 06].
47. Kurtzke JF. Epidemiology and etiology of multiple sclerosis. Phys Med Rehabil Clin N Am 2005;16:327-49.
48. Libon F, Cavalier E, Nikkels AF. Skin color is relevant to Vitamin D synthesis. Dermatology 2013;227:250-4.
49. Lizak N, Lugaresi A, Alroughani R, Lechner-Scott J, Slee M, Havrdova E, *et al.* Highly active immunomodulatory therapy ameliorates accumulation of disability in moderately advanced and advanced multiple sclerosis. J Neurol Neurosurg Psychiatry 2017;88:196-203.
50. Lizán L, Comellas M, Paz S, Poveda JL, Meletiche DM, Polanco C, *et al.* Treatment adherence and other patient-reported outcomes as cost determinants in multiple sclerosis: A review of the literature. Patient Prefer Adherence 2014;8:1653-64.
51. Lorefice L, Fenu G, Pitzalis R, Scalas G, Frau J, Coghe G, *et al.* Autoimmune comorbidities in multiple sclerosis: What is the influence on brain volumes? A case-control MRI study. J Neurol 2018;265:1096-101.
52. Marck CH, Neate SL, Taylor KL, Weiland TJ, Jelinek GA. Prevalence of comorbidities, overweight and obesity in an international sample of people with multiple sclerosis and associations with modifiable lifestyle factors. PLoS One 2016;11:e148573.
53. Markowitz CE. Multiple sclerosis update. Am J Manag Care 2013;19:s294-300.
54. Marrie R, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T, *et al.* Comorbidity, socioeconomic status and multiple sclerosis. Mult Scler 2008;14:1091-8.
55. Marrie RA, Cohen J, Stuve O, Trojano M, Sørensen PS, Reingold S, *et al.* A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: Overview. Mult Scler 2015;21:263-81.
56. Marrie RA, Cutter G, Tyry T, Campagnolo D, Vollmer T. Smoking status over two years in patients with multiple sclerosis. Neuroepidemiology 2009;32:72-9.
57. Marrie RA, Cutter G, Tyry T, Vollmer T. A cross-sectional study of bone health in multiple sclerosis. Neurology 2009;73:1394-8.
58. Marrie RA, Cutter GR, Tyry T, Cofield SS, Fox R, Salter A, *et al.* Upper limb impairment is associated with use of assistive devices and unemployment in multiple sclerosis. Mult Scler Relat Disord 2017;13:87-92.
59. Marrie RA, Horwitz R, Cutter G, Tyry T. Cumulative impact of comorbidity on quality of life in MS. Acta Neurol Scand 2012;125:180-6.
60. Marrie RA, Horwitz RI, Cutter G, Tyry T, Vollmer T. Association between comorbidity and clinical characteristics of MS. Acta Neurol Scand 2011;124:135-41.
61. Marrie RA, Horwitz RI, Cutter G, Tyry T, Vollmer T. Smokers with multiple sclerosis are more likely to report comorbid autoimmune diseases. Neuroepidemiology 2011;36:85-90.
62. Marrie RA, Miller A, Sormani MP, Thompson A, Waubant E, Trojano M, *et al.* Recommendations for observational studies of comorbidity in multiple sclerosis. Neurology 2016;86:1446-53.
63. Marrie RA, Reider N, Stuve O, Trojano M, Sorensen PS, Cutter GR, *et al.* The incidence and prevalence of comorbid

gastrointestinal, musculoskeletal, ocular, pulmonary, and renal disorders in multiple sclerosis: A systematic review. Mult Scler 2015;21:332-41.
64. Marrie RA, Rudick R, Horwitz R, Cutter G, Tyry T, Campagnolo D, *et al.* Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis. Neurology 2010;74:1041-7.
65. Marrie RA, Yu BN, Leung S, Elliott L, Caetano P, Warren S, *et al.* Rising prevalence of vascular comorbidities in multiple sclerosis: Validation of administrative definitions for diabetes, hypertension, and hyperlipidemia. Mult Scler 2012;18:1310-9.
66. Mattei J, Tamez M, Ríos-Bedoya CF, Xiao RS, Tucker KL, Rodríguez-Orengo JF, *et al.* Health conditions and lifestyle risk factors of adults living in Puerto Rico: A cross-sectional study. BMC Public Health 2018;18:491.
67. Miranda MT, Suárez E, Abbas M, Chinea A, Tosado R, Mejías IA, *et al.* HLA class I; II alleles in multiple sclerosis patients from Puerto Rico. Bol Asoc Med P R 2013;105:18-23.
68. Morran MP, Vonberg A, Khadra A, Pietropaolo M. Immunogenetics of Type 1 diabetes mellitus. Mol Aspects Med 2015;42:42-60.
69. Morrow SA, Drake A, Zivadinov R, Munschauer F, Weinstock-Guttman B, Benedict RH, *et al.* Predicting loss of employment over three years in multiple sclerosis: Clinically meaningful cognitive decline. Clin Neuropsychol 2010;24:1131-45.
70. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 2006;296:2832-8.
71. Newland P, Wagner JM, Salter A, Thomas FP, Skubic M, Rantz M, *et al.* Exploring the feasibility and acceptability of sensor monitoring of gait and falls in the homes of persons with multiple sclerosis. Gait Posture 2016;49:277-82.
72. O'Connor RJ, Cano SJ, Ramió i Torrentà L, Thompson AJ, Playford ED. Factors influencing work retention for people with multiple sclerosis: Cross-sectional studies using qualitative and quantitative methods. J Neurol 2005;252:892-6.
73. Olek MJ. Disease-modifying Treatment of Relapsing-remitting Multiple Sclerosis in Adults. UpToDate; 2016. Available from: https://www.uptodate.com/contents/disease-modifying-treatment-of-relapsing-remitting-multiple-sclerosis-in-adults. [Last accessed on 2019 Mar 04].
74. Olivera EJ, Palacios C. Use of supplements in puerto rican older adults residing in an elderly project. P R Health Sci J 2012;31:213-9.
75. Paparrigopoulos T, Ferentinos P, Kouzoupis A, Koutsis G, Papadimitriou GN. The neuropsychiatry of multiple sclerosis: Focus on disorders of mood, affect and behaviour. Int Rev Psychiatry 2010;22:14-21.
76. Patti F. Optimizing the benefit of multiple sclerosis therapy: The importance of treatment adherence. Patient Prefer Adherence 2010;4:1-9.
77. Perreira K, Peters R, Cafarella Lallemand N, Stephen Z. Puerto Rico Health Care Infrastructure Assessment: Site Visit Report. Puerto Rico; 2017. Available from: https://www.urban.org/research/publication/puerto-rico-health-care-infrastructure-assessment-site-visit-report/view/full_report. [Last accessed on 2017 Jan 11].
78. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European study group on interferon beta-1b in secondary progressive MS. Lancet 1998;352:1491-7.
79. Polman CH. Medicine Cabinet. US Patent, No. 4,663,621 2000;173:398-402. Available from: http://www.google.com/patents/US4663621. [Last accessed on 2019 Feb 06].
80. Ramírez-Vick M, Hernández-Dávila L, Rodríguez-Rivera N, López-Valentín M, Haddock L, Rodríguez-Martínez R, *et al.* Prevalence of Vitamin D insufficiency and deficiency among young physicians at university district hospital in san juan, Puerto Rico. P R Health Sci J 2015;34:83-8.
81. Rao SM, Leo GL, Ellington L, Nauertz T, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. Neurology 1991;41:692-6.
82. Reich DS, Lucchinetti CF, Calabresi PA. Multiple sclerosis. N Engl J Med 2018;378:169-80.
83. Reider N, Salter AR, Cutter GR, Tyry T, Marrie RA. Potentially modifiable factors associated with physical activity in individuals with multiple sclerosis. Res Nurs Health 2017;40:143-52.
84. Rico P, Care H, Perreira K, Peters R, Lallemand N, Zuckerman S. Rese Arch Report Site Visit Report; 2017. Available from: https://www.urban.org/sites/default/files/publication/87011/2001050-puerto-rico-health-care-infratructure-assessment-site-visit-report_1.pdf. [Last accessed on 2019 Jan 14].
85. Roessler RT, Rumrill PD, Li J, Daly K, Anhalt K. High-priority employment concerns of hispanics/latinos with multiple sclerosis in the United States. J Vocat Rehabil 2016;45:121-31.
86. Roman J. The Puerto Rico healthcare crisis. Ann Am Thorac Soc 2015;12:1760-3.
87. Salter A, Thomas N, Tyry T, Cutter G, Marrie RA. Employment and absenteeism in working-age persons with multiple sclerosis. J Med Econ 2017;20:493-502.
88. Santa ML. Diabetes Mellitus in Puerto Rico: Opportunities to be Discovered Ciencia Puerto Rico. Cienc. Puerto Rico; 2016. Available from: https://www.cienciapr.org/en/blogs/conocimiento-tu-salud/diabetes-mellitus-puerto-rico-opportunities-be-discovered. [Last accessed on 2019 Mar 07].
89. Sayre RM, Dowdy JC. Darkness at noon: Sunscreens and Vitamin D3. Photochem Photobiol 2007;83:459-63.
90. Smith MM, Arnett PA. Factors related to employment status changes in individuals with multiple sclerosis. Mult Scler 2005;11:602-9.
91. Stoppe M, Busch M, Krizek L, Then Bergh F. Outcome of MS relapses in the era of disease-modifying therapy. BMC Neurol 2017;17:151.
92. Tanasescu R, Constantinescu CS, Tench CR, Manouchehrinia A. Smoking cessation and the reduction of disability progression in multiple sclerosis: A cohort study. Nicotine Tob Res 2018;20:589-95.
93. Tettey P, Simpson S Jr., Taylor BV, van der Mei IA. The co-occurrence of multiple sclerosis and Type 1 diabetes: Shared aetiologic features and clinical implication for MS aetiology. J Neurol Sci 2015;348:126-31.
94. Van Dyne EA, Neaterour P, Rivera A, Bello-Pagan M, Adams L, Munoz-Jordan J, *et al.* Incidence and outcome of severe and nonsevere thrombocytopenia associated with zika

virus infection-Puerto Rico, 2016. Open Forum Infect Dis 2019;6:ofy325.
95. Vijayasingham L, Jogulu U, Allotey P. Work change in multiple sclerosis as motivated by the pursuit of illness-work-life balance: A qualitative study. Mult Scler Int 2017;2017:1-7. Available from: https://www.hindawi.com/journals/msi/2017/8010912. [Last accessed on 2019 Feb 06].
96. Wallin MT, Culpepper WJ, Campbell JD, Nelson LM, Langer-Gould A, Marrie RA, *et al.* The prevalence of MS in the United States: A population-based estimate using health claims data. Neurology 2019;92:e1029-40.
97. Weinstock-Guttman B, Zivadinov R, Horakova D, Havrdova E, Qu J, Shyh G, *et al.* Lipid profiles are associated with lesion formation over 24 months in interferon-β treated patients following the first demyelinating event. J Neurol Neurosurg Psychiatry 2013;84:1186-91.
98. Wright NC, Looker AC, Saag KG, Curtis JR, Delzell ES, Randall S, *et al.* The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. J Bone Miner Res 2014;29:2520-6.
99. Zarei S, Eggert J, Franqui-Dominguez L, Carl Y, Boria F, Stukova M, *et al.* Comprehensive review of neuromyelitis optica and clinical characteristics of neuromyelitis optica patients in Puerto Rico. Surg Neurol Int 2018;9:242.
100. Ziemssen T, Derfuss T, de Stefano N, Giovannoni G, Palavra F, Tomic D, *et al.* Optimizing treatment success in multiple sclerosis. J Neurol 2016;263:1053-65.

How to cite this article: Zarei S, Maldonado I, Franqui-Dominguez L, Rubi C, Rosa YT, Diaz-Marty C, *et al*. Impact of delayed treatment on exacerbations of multiple sclerosis among Puerto Rican patients. Surg Neurol Int 2019;10:200.