Characterization of Patients with Amyotrophic Lateral Sclerosis attending the Muscular Dystrophy Association–Supported Clinics in Puerto Rico

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Objective: To evaluate the sociodemographic characteristics and clinical and functional profile of amyotrophic lateral sclerosis (ALS) patients evaluated at Puerto Rico's Muscular Dystrophy Association–supported (MDA) clinics.

Methods: A retrospective review of 76 medical records of ALS patients evaluated at any of four MDA-sponsored clinics in Puerto Rico.

Results: The mean age of diagnosis was 57.4 ± 11.1 yrs. Most of the patients (52.3%) were women. The majority of the cases were sporadic (48.7%). Over 40% of the patients were diagnosed at one year or earlier. Patients with initial upper extremity involvement (63.2%) were diagnosed earlier (≤ 6 months) than any of the others. The most common presentation of the disease overall was lower extremity weakness (34.2%), which was followed by a bulbar presentation (31.6%). There was a marked difference between men and women in disease presentation, with bulbar involvement in 75% of the women.

Conclusion: This study characterized a sample of ALS patients in Puerto Rico who are receiving services at the MDA-sponsored clinics. Puerto Rican patients have similarities with published data from the United States and other countries, including: sporadic pattern, initial symptoms in extremities, and time to diagnosis. Major differences are that the disease was more common in women than in men and that a higher than expected percentage of patients presented with bulbar onset. This may partly account for the overall predominance of the disease in women over men as found in our study, since the bulbar presentation has been reported to be more common in women. Studies with a greater number of patients are needed to determine whether our findings are reproducible. This study will serve as a basis for designing future analytic studies regarding etiology or the factors that might modulate disease progression. [*P R Health Sci J 2018;37:5-11*]

Key words: Amyotrophic Lateral Sclerosis, ALS Clinical Presentation, ALS in Puerto Rico

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive, fatal neurodegenerative disease that affects the motor neurons and for which no cure has been found. ALS progresses very rapidly, and patients afflicted with it have a life expectancy of 1 to 5 years after diagnosis. There is still no identifiable cause for the disease, which has hindered the finding of an effective treatment. At this time, the only FDA-approved medication available for the treatment of ALS is riluzole, which has been shown to prolong survival for only about 2 months (1). The American Academy of Neurology has established guidelines to provide uniform and adequate supportive care for ALS patients. These are being used by neurologists, physiatrists, and neuromuscular specialists around the United States (US) (2, 3).

ALS has been increasingly recognized as a disorder with a multifactorial etiology (4). There are some data available suggesting a few risk factors for the development of ALS, including age and smoking habits (5, 6). A large study of ALS incidence in Italy showed that the peak onset of the disease for men fell in the 75 to 79 year age range and for women in the 70 to 74 year age range (7). Most cases of ALS are sporadic, but a genetic link has been identified in about 10% of all cases

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(8). Genetic modifiers, particular to each individual, could be responsible for the variety of symptoms in certain individuals exposed to similar environments, for the different initial presentations of the disease, and even for the different rates of disease progression in individuals.

ALS is not a nationally notifiable condition, which limits the epidemiologic data available. For instance, worldwide incidence rates are variable. In a literature review published by Brooks (9) in 1996, an estimated incidence in North America of 1.4 to 2.0 patients per 100,000 per year, as opposed to the 0.6 to 0.7 patients per 100,000 per year in Mediterranean countries, was reported. Logroscino et al. (10) later reported that the incidence in the US was about 1.5 to 2.5 cases each year for every 100,000 habitants. Whether there is variability of ALS frequency in different ethnicities is still a controversy, and has been so for decades (10). Available epidemiologic data suggest that the incidence of ALS is lower among African, Asian, and Hispanic ethnicities than it is in Caucasians (11). Even in the US, the under-ascertainment of neurodegenerative diseases in ethnic minorities may account for the apparent racial variation in ALS frequency (12).

More recent studies have focused on prevalence differences, due to the unavailability of accurate dates of diagnosis in some of the data sources, such as those that make use of patient-entered data. A recent study published in July 2014 by the Centers for Disease Control and Prevention (CDC) reported that the prevalence of ALS in the US from 2010 to 2011 was 3.9 cases per 100,000 habitants in the general population (13).

The clinical presentation of ALS is heterogeneous. As a consequence, its diagnosis is often delayed by months or even years. A study in Minnesota revealed that the mean time from symptom onset to diagnosis was 13 months (14). The progressive death of motor neurons in the brain and in the spinal cord accounts for the clinical manifestations of ALS, which are a combination of weakness and atrophy (lower motor neuron symptoms), as well as a loss of inhibitory function usually performed by motor neurons in the brain (upper motor neuron symptom). Patients may present with difficulty walking, swallowing, speaking, or grabbing objects. Eventually, the respiratory muscles become involved, causing respiratory failure and death.

Diagnosis is mostly done on the basis of the clinical findings. Ancillary tests including imaging studies, blood tests, and electrodiagnostic studies (nerve conduction studies and electromyography (15)) are done to exclude alternative diagnoses. Toxic exposure, physical trauma, and strenuous exercise, among other exogenous factors, have been viewed as potential concerns in terms of an individual's propensity for developing sporadic ALS; however, up to now, studies have reported conflicting results.

To this date, no registry is available for ALS patients in Puerto Rico. Thus, the incidence and prevalence of this disease in Puerto Rico are still unknown. Patients with ALS are usually diagnosed and followed by neurologists and neuromuscular medicine subspecialists. In Puerto Rico, there are four clinics that are supported by the Muscular Dystrophy Association (MDA) and that provide care to these patients. Most of the patients on the island suffering from ALS are evaluated in one of these clinics. The clinics cover a broad geographical area of Puerto Rico and are specialized clinics to which this type of patient is referred for evaluation, diagnostic studies, and treatment. Specifically, the clinics are located in Ponce (1 clinic in the south), San Germán (1 clinic in the west), and Río Piedras (2 clinics in the north). Additionally, assistive equipment and services that benefit ALS patients are also provided at these clinics. These are the reasons why, at some point, the majority of ALS cases in Puerto Rico are evaluated at the MDA clinics.

Study aim

The aim of this study was to characterize ALS patients served by the MDA clinics in terms of their sociodemographic, clinical, and functional characteristics. Due to the scarcity of data on ALS on the island, this study represents a first step towards understanding the sociodemographic characteristics and clinical and functional profile of ALS patients attending these clinics in Puerto Rico. The information derived from this study will serve as a basis for designing future analytic studies regarding the etiology of ALS in the Puerto Rican population.

Methods

This study was approved by the IRB of the University of Puerto Rico, Medical Sciences Campus (IRB protocol number: 7090113). The study consisted of a retrospective review of the medical records of ALS patients attending the MDA clinics in Puerto Rico during the years of 2004 to 2014.

The clinic director or co-director at each site granted permission to the investigators to review all the medical records of patients diagnosed with ALS. The patient coordinator from the MDA clinics provided to each clinical director or co-director a list of all the medical records of registered patients who were classified as ALS patients on their first evaluation at one of the MDA clinics. Records from each of the four MDA clinics in Puerto Rico were evaluated on site.

The data collected from the medical records included age, gender, place of birth and of current residency, occupation, toxic habits, date of initial evaluation, time to diagnosis, age at the time of diagnosis, history of trauma to head or neck, involvement in sports, family medical history, comorbidities, medications used, electrodiagnostic and imaging studies, history of spine surgery, clinical presentation, functionality of upper extremities on initial visit, functionality of lower extremity on initial visit, functionality at the time of last clinical evaluation, and measures of/devices to support breathing or swallowing. Limb functionality was defined using a manual muscle test (MMT), with a score greater than 3 (out of 5) being functional and a score lower than 3 (out of 5) being not functional. Data obtained from medical records were collected on a separate

log sheet containing no information that could potentially link patients' identifiers with the collected information. A total of 78 records were reviewed; 2 had to be excluded from the analysis because of incomplete data, leaving a total of 76 patients. For the analysis of progression of weakness, patients with only one visit were excluded.

Statistical analysis

Data are prsented as mean ± SD for continuous variables and as frequency distributions for categorical variables. All data management and statistical analyses were performed using Stata for Windows release 13.0 (StataCorp, College Station, Texas).

Results

Sociodemographic characteristics

Age and Gender

The mean age at diagnosis was 57.2 ± 11.1 years (minimum of 24 and maximum of 77). Over half (52.6%) of the patients were women (Table 1).

Table 1. Demographic of ALS patients

Gender	Number	Percent (%)
Women	40	52.6
Men	36	47.4
Mean age at diagnosis	57.2 ± 11.1 years (min: 24, max: 77)	

Geography

Four percent of ALS patients lived in the municipalities of Arecibo, Bayamón, and Caguas (encompassing the northwestern to the northeastern regions). Five percent (5.3%) of the patients lived in the municipality of San Sebastián (western region), and the highest percentage of patients (14.7%) was from the municipality of San Juan (urban area).

Employment

Information regarding employment status at the time of a given patient's first visit revealed that only 36.8% had been asked about his or her employment status. Of those, only 1.3% were working at the time of their first visit. Of the cases that listed prior work information, 5.3% had worked on an assembly line, followed by 4% who had worked as environmental consultants, and electricians, janitors, secretaries, housewives, and engineers with 2.6% of patients in each category.

Clinical characteristics

Toxic habits

Although most of the patients (59.2%) did not have data about their toxic habits, those who had reported them, for the most part, denied using alcohol, tobacco, or any illicit drugs (15.8%) (Table 2). The patients who admitted using tobacco made up 10.5% of the sample.

Table 2. Current toxic habits of ALS patients

	Number	Percent (%)
Alcohol	7	9.5
Tobacco	8	10.5
Illicit drugs	1	1.3
Alcohol + Tobacco + Illicit drugs	1	1.3
Alcohol + Tobacco	2	2.6
None	12	15.8
Unknown	45	59.2

Family history

A family history was not available in 47.4% of the cases, and 48.7% of the patients did not have a family history of ALS. In patients reporting a family history of ALS (4%), the family member most commonly affected with the disease was the mother (2.6%).

Comorbidities

The most frequently reported comorbidity was hypertension (40.8%) (Table 3). Diabetes was less frequent, with only 18.7% of the cases reporting having it. Although 27.6% of the records lacked information about prior immunosuppression, of the remaining patients, 65.8% had not undergone any prior immunosuppressive treatment. Similarly, information about cervical MRI studies was missing in 44.7% of the cases. Nonetheless, some type of abnormality was evident in 35.5% of the documented cases. Nearly 20% of the cases did not show any abnormalities in cervical MRI.

Table 3. Comorbidities of ALS patients

	Number	Percent (%)
Hypertension	31	40.8
Type II diabetes mellitus	14	18.7
Thyroid disease	9	11.8
Cancer	2	2.6
Hypercholesterolemia	14	18.4

Trauma

Information about trauma to the neck was not available for 79% of the cases. Of the cases asked about this type of trauma, 17.1% denied having experienced it, while 4% admitted to having suffered some kind of trauma to the neck in the past.

Similarly, data for head trauma was not detailed in 79% of our records. According to the available data, there was a past history of head trauma in 2.6% of the patients, while 18.4% denied having suffered any type of trauma to the head.

Time to diagnosis

The time from the onset of symptoms to the time of diagnosis was 1 year or less in 42.1% of the cases, followed by 26.3% that were diagnosed from 1 to 2 years after the onset of the symptoms (Table 4). According to the presentation of the disease the time to diagnosis varied as follows: of the ones presenting with upper

extremity weakness, 63.2% were diagnosed in less than 6 months; of those with lower extremity weakness, 34.6% were diagnosed in less than 6 months and 26.9% in 6 months, or more but less than 1 year.

A similar percentage (26.9%) was diagnosed after a longer period of time (1.5 – 2 years) when the presentation was in the legs. When the presentation was bulbar, 45.8% of the cases were diagnosed within 6 months of the onset of symptoms and 37.5% were diagnosed at 6 months or later (up to 1 year). Other presentations (42.9% of the cases), such as mixed upper and lower extremity pain, bulbar palsy and upper extremity pain, and unknown, were diagnosed mostly in from 1 to 1.5 years.

Table 4. Time to diagnosis of ALS patients

	Number	Percent (%)
≤ 1 year	32	42.1
>1 but ≤ 2 years	20	26.3
>2 but < 3 years	6	7.9
≥ 3 years	12	15.8
Unknown	6	7.9

Clinical presentation

The presentation of the disease was mostly in the lower extremities (34.2%), followed by bulbar presentation (31.6%) and weakness restricted to the upper extremities (25%) (Table 5). The differences in disease presentation between men and women were as follows: 36.8% of the women presented with weakness restricted to the upper extremities, while 63.2% of men presented with the same; lower extremity weakness as the initial symptom was equally distributed (50/50) between both women and men; bulbar presentation was noted in 75% of the women but in only 25% of men.

Table 5. Clinical presentation of weakness of ALS patients

	Number	Percent (%)
Upper extremities	19	25.0
Lower extremities	26	34.2
Bulbar	24	31.6
Upper + Lower extremities	3	4.0
Bulbar + Upper extremities	1	1.3
Unknown	3	4.0

Functionality of limbs at the time of initial evaluation

At the time of their initial evaluations in our clinics, 86.8% of the patients had functional arm strength, and 85.5% had a functional strength in their legs. At the time of their last visit, 61.8% of patients had functional arm strength, 34.2% did not have any functional strength in their arms, and in 4% of the cases arm strength was unknown. At the time of the final evaluation, the lower extremities were functional in 55.3% of the patients; 43.4% did not have any functional strength; and the strength of 1.3% of our sample was unknown. When the relative strengths of both the upper and lower limbs were compared, 77.6% of the patients had functional strength in all their extremities on initial evaluation, 17.1% had no dysfunction in either their arms or their legs, and 5.3% had dysfunction in all 4 extremities.

Diagnostic studies

Most of the patients had an electrodiagnostic study done for the purposes of diagnosis, the results of which were included in 69.7% of the medical records. Most of the cases (34.2%) needed only one study for the diagnosis, but a significant percentage (30.3%) of the cases required more than one study for diagnosis.

Treatment with Riluzole

Riluzole was being taken by 56.6% of the patients. However, 18.4% of the records did not have information about the riluzole use of the patients being described within.

Invasive procedures

At the time of initial evaluation, 90% of the patients had not had any invasive procedures (tracheostomy or gastrostomy). Of the remaining 10%, 5.3% had undergone a percutaneous endoscopic gastrostomy (PEG), 2.6% had undergone both a PEG and a tracheostomy, and 1.3% had undergone a tracheostomy only.

In terms of respiratory care, at the time of the final evaluation, invasive respiratory procedures had already been on done or recommended for 5.3% of patients. Of those, 46.5% were using noninvasive ventilation and 43.4% were not using any respiratory device; in 5.3% of the cases, this information was not known.

At the time of the last evaluation, 39.5% of the patients had had an invasive procedure for feeding (PEG) done or recommended and 56.6% had not had any such procedure; in 4% of the cases, this information was not known.

Discussion

Our results slightly differ from the published data from one of the largest studies in the US, which was based on a national database and self-reported data from ALS patients (13). Their highest overall prevalence of the disease was in the age group of 70 to 79 years when the data were based on the national database, but when only the self-reported data were considered, the highest prevalence was in the group of 50- to 59-year-olds. The latter is consistent with our results, which showed that the mean age of diagnosis in our study sample was 57.2 years. Other studies have consistently reported that the highest prevalence of ALS is in the group of patients aged from 70 to 79 years (16). In our study we found that women were more commonly affected with ALS than men, and these results are different from previously published data which established that ALS was slightly more common in men than in women (ratio of 1.6:1) (13).

In terms of the geographical distribution of the disease, in our study the affected patients were more commonly living in the urban area of the island. Although there are four MDA clinics that cover three of the four cardinals points of the island, these

results might indicate that the patients living in the island's urban area have greater levels of health literacy and easier access to specialized clinics.

Of the patients that reported their employment (37%), the disease was more prevalent in those having non-professional jobs. Previous studies have shown conflicting data about occupation and the risk of developing ALS, but in a study by Sutedja et al. (17) that involved a systematic review of the literature, it was reported that veterinarians, athletes, hairdressers, power-production plant operators, and members of the armed forces appeared to have an increased risk of ALS. Older studies have also reported that individuals who work in places where exposure to magnetic fields is increased or where there is exposure to electric shock are at increased risk for developing ALS (18). It was shown in one study that patients with a history of blue collar jobs, such as welders, had an increased risk of developing ALS although the finding was not statistically significant (19).

Regarding toxic habits, in our study ALS was more prevalent in patients without a history of toxic habits. The second more prevalent group was the group of patients that admitted having a history of smoking. However, our data were obtained from medical records that asked about current use of tobacco but not past use. Therefore, a negative response to tobacco use at the time of the evaluation does not necessarily exclude past exposure, and we cannot be certain that current non-smokers did not have any exposure in the past. Prior studies have found an association between ever smoking cigarettes and an increased risk of ALS (5, 17).

The majority of our medical records did not have information about history of trauma to the head or neck, but those that did have such information showed that most patients denied having experienced this type of trauma. Trauma has been one of the mechanisms that could potentially be identified as a risk factor for the development of ALS. Many studies suggest trauma as a possible trigger for the disease, but these have not been able to establish it as a definite risk factor (19, 20). The association between physical exertion and the development of ALS also remains elusive because of the current lack of powerful epidemiologic support or a proven pathogenic mechanism (5).

In terms of family history of ALS, the majority of our patients did not have a family member who had been diagnosed with the disease. This is consistent with Mitsumoto's study (8), in which only 10% of the patients had a positive family history.

Similar to a study published by Sorenson et al. (14) that reported a mean time from symptom onset to diagnosis of 13 months, our study showed that for the majority of the patients, a diagnosis was made in a period of 12 months or less. It is in our interest to point out that there is a variation in the time to diagnosis that depends on the area of the body involved at the presentation of the disease. Patients that presented with upper limb weakness were diagnosed with ALS earlier than those who presented with bulbar symptoms, which latter were in turn diagnosed earlier than were those with a presentation of leg weakness.

The most commonly reported comorbidities in our study were hypertension and type 2 diabetes mellitus, but this information might be biased since these are the most frequent diseases asked by physicians when the patients are interviewed. In addition, these are diseases with a high prevalence in the Hispanic and Puerto Rican populations. Few studies have addressed the possible relationship between diabetes mellitus and the risk of ALS. Interestingly, one of the few studies assessing comorbidities related to ALS found that type 2 diabetes provided a protective effect for the development of ALS (21).

In accordance with our study, it has been reported that motor neuron dysfunction typically begins in one limb, either upper or lower (80%), or one region of the spinal cord (cervical/lumbar), and less frequently in the bulbar area (20%). Of these presentations, only the bulbar presentation has been reported to be more common in women (ratio of 1.9:1) (22). In a study performed in 1985 with US military veterans with a diagnosis of ALS, weakness onset in one of the limbs was reported in 76% of the cases, and it was associated with longer survival rates compared with those of patients with non-extremity sites of onset (22, 23).

The significant percentage of patients not using riluzole documented in our study, despite its being the only available FDA-approved treatment, might be in part related to the limited effectiveness of the medication, which has been reported to increase lifespan by only three months. In spite of this increase in survival, the disease course continues to be highly variable, even after the treatment with riluzole has begun. We think that this is influencing patients' decisions not to undergo treatment with riluzole or to discontinue such treatment after having undergone it for a period of time.

Studies consistently report an average disease duration of three years from the onset of symptoms, but this can vary significantly. Patients usually die of respiratory failure. We could not assess the speed of progression of the patients in our group because of differences in the data gathered and our inability to prospectively collect information for the purposes of this study.

The data presented in our study, as function of arm and legs at initial visit and final visit, were limited because of differences in the times that elapsed between the first and last appointments for the patients. If groups of patients were to be further divided for the purpose of the analysis, such a division would affect the interpretation because of the resulting small size of the samples. This has been a significant limitation in the development of protocols to evaluate effectiveness of new therapies, which is why the multi-centric study approach is currently favored in the ALS field. Another limitation of this study is the absence of important screening information in old medical records (for example, history of exposure to smoking habits, involvement in sports, and past trauma) to assess risk factor for ALS. Our hope is that electronic records will facilitate information gathering and uniform data collection. Prospective studies and the creation of a database that can collect information from patients for more extended periods of time would greatly

enhance this possibility. In our clinics, we have implemented the use of the ALS Functional Rating Scale in order to provide a more uniform method of disease progression on every visit, or at least at designated time intervals. This validated scale for rating the progression of the disease will greatly enhance the data collected in future studies.

Unfortunately, at this point we are not able to determine whether our data would be altered if we were to take into account the ALS patients that were not being evaluated at one of the MDA clinics and that might have different sociodemographic or clinical profiles. One important consideration would be to determine whether a given prognosis would be altered in any one or more of these non-MDA patients, which are not evaluated or treated in a multidisciplinary setting, such as one of our MDA clinics. Studies have shown that patients treated in multidisciplinary clinics have improved quality of life and improved survival rates (23, 24).

Conclusion

ALS is still considered a rare disease. This study is a first attempt to describe the sociodemographic characteristics and clinical and functional profile of ALS patients in the MDA clinics in Puerto Rico. More patients are needed in order to determine whether the clinical profile of patients that do not receive services at MDA clinics differs from our current results. It is important to further evaluate whether, although there are practice parameters regarding the care of patients with ALS, non-MDA patients are managed according to the established criteria. The trend of our collected data suggests that there are more similarities than differences in our population when compared to studies published from other countries and the US.

Resumen

Objetivo: Evaluar las características sociodemográficas y perfil funcional y clínico de los pacientes con Esclerosis Lateral Amiotrófica (ELA) que son atendidos en las clínicas de la Asociación de Distrofia Muscular (ADM) de Puerto Rico. Métodos: Revisión retrospectiva de 76 expedientes médicos de pacientes de ALS atendidos en las cuatro clínicas de la ADM de Puerto Rico. Resultados: La edad media al momento del diagnóstico fue 57.4 ± 11.1 años, y más de la mitad de los pacientes (52.3%) eran mujeres. Aproximadamente la mitad (48.7%) de los pacientes fueron esporádicos. La mayoría de los pacientes fueron diagnosticados en ≤ 1 año (42.1%). Pacientes con envolvimiento inicial de extremidad superior fueron diagnosticados más temprano (≤ 6 meses) (63.2%). La presentación más común fue debilidad de extremidades inferiores (34.2%), seguido por una presentación bulbar (31.6%). Se observó una marcada diferencia de género en la presentación de la enfermedad con la manifestación bulbar en un 75% de las mujeres. Conclusión: Este estudio muestra las características clínicas de los pacientes de ALS en las clínicas de la ADM en Puerto Rico. Los pacientes puertorriqueños tienen similitudes con los datos publicados en los Estados Unidos y otros países, incluyendo el patrón esporádico, síntomas iniciales en las extremidades y el tiempo para hacer el diagnóstico. La diferencia principal es que la enfermedad es más común en las mujeres y un porcentaje mayor al esperado de pacientes que presentaron con síntomas bulbares. Esto podría explicar parcialmente el predominio de mujeres encontrado en nuestro estudio ya que sólo la presentación bulbar ha sido reportada como más común en mujeres. Estudios con un número mayor de pacientes será necesario para evaluar si nuestros hallazgos son reproducibles. Este estudio servirá de base para el diseño de estudios futuros de análisis, con respecto a la etiología o factores que puedan modular la progresión de la enfermedad.

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