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FEEDBACK INTERACTION OF RESEARCH, ADVOCACY, AND CLINICAL CARE APPLIED TO ALS RESEARCH IN SOUTH AMERICA

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease causing motor neuron loss and weakness. Worldwide prevalence is 4–6/100,000. Incidence is 1.5–2.7/100,000 per year and may be increasing. Studies suggest race and ethnicity affect the prevalence and incidence of ALS.[1] Understanding the impact of these variables on disease incidence could provide important insight into ALS determinants. A major roadblock for comparison across populations is the lack of epidemiologic data about ALS from many underdeveloped regions. In these regions, ALS is often undertreated due to health care disparities. This article discusses challenges for ALS research in South America (SA) and examines the ALS scientific record to explore the interactions and synergies of research, clinical care, and patient advocacy in underdeveloped regions.

Introduction to South America's challenges for ALS research. SA has a population of approximately 400 million inhabiting 12 countries and 2 protected territories. Approximately 54% of the SA population resides in Brazil, followed by Colombia (13%), Argentina (11%), Peru (8%), Chile (5%), Ecuador (4%), Bolivia (3%), Paraguay (2%), Uruguay (1%), Guyana (0.2%), and Suriname (0.1%) (Venezuela lacks census data). Throughout SA, there are large disparities in resources and health care utilization.

Many of these countries face social inequalities and a scarcity of medical resources. According to the World Health Organization (WHO), the ratio of neurologists to population in the Americas is 0.89 per 100,000 individuals, a statistic skewed by data from the United States, Canada, and Brazil (~5.2, 1.44, and 1.42 neurologists/100,000, respectively) (WHO). In the remaining SA countries, the ratio is considerably less than 1 neurologist per 100,000 individuals (Colombia 0.75, Peru 0.78, Ecuador 0.87, Bolivia 0.5, and Chile 0.54 per 100,000; data from SA neurologist associations).

As an initial assessment of the impact of ALS research in SA, we conducted a survey of ALS literature. ALS scientific output found large disparities in ALS research throughout SA, reflecting medical resource inequities.

Analysis of ALS literature in SA over the last 30 years reveals significant regional variations in publication rates. Although the number of ALS publications steadily increased from 1977 to 2012, we found a negligible total count of ALS articles (225). Brazil accounts for 116, followed by Argentina, Uruguay, and Chile (53, 30, and 20 articles, respectively). Other countries had few to no publications during the same period. Although the majority of ALS publications from SA are written in English, 72 publications were in Portuguese or Spanish and published in regional or local journals, limiting their global influence.

Lacking direct indicators, we used ALS publications to estimate research activity and clinical care quality. Reports about ALS management exist from Brazil and Argentina: mean time of diagnosis after initial symptoms was 16.6–18 months, approximately 4 months longer than that reported in developed nations[2]; in Brazil, survival was reported at 30–48 months and in Argentina <17 months with the use of noninvasive ventilation and riluzole and <11 months with supportive treatment alone[3,4]; in 2000, riluzole, the only disease-modifying therapy for ALS, was prescribed in 23%–67% of cases.[2] The cost of riluzole in SA varies ($600–$1,600/month) and is seldom covered by a government subsidy. Riluzole has been shown to slow disease progression, extending survival by at least 3 months, and longer in some observational studies.

ALS multidisciplinary care clinics are associated with better clinical outcomes, including increased survival. We were unable to identify ALS clinics in any country, though neuromuscular clinics exist. Consistent with limited disease management, ALS epidemiologic data in SA are also scarce and lack appropriate controls.[1]

Concerted effort of ALS research, clinical care, and patient advocacy in the United States. In sharp contrast to SA, the number of publications in the United States during 1977–2012 was exponentially higher (>3,600). The US publication rates increased significantly in

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Figure Publication record of the United States reveals 3 important years for ALS research

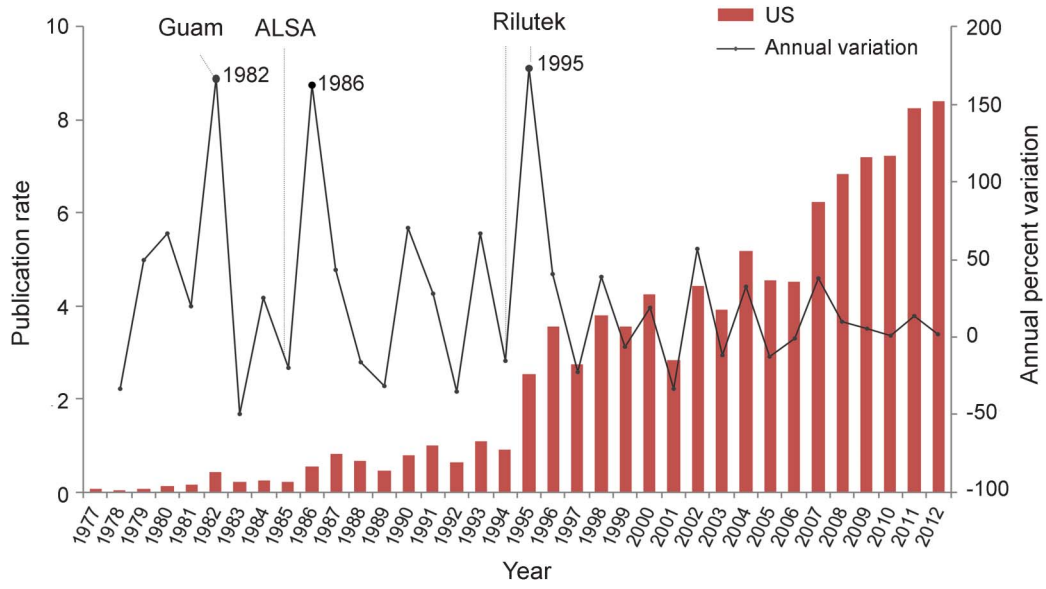

Chart represents the annual rate of amyotrophic lateral sclerosis (ALS) publications in the United States (red bars) for 1977–2012. A MEDLINE search was performed using the advanced search option with the medical subject heading tag and "Amyotrophic Lateral Sclerosis" and "USA" or "United States" (same search strategy was followed for each country in South America in MEDLINE + LILACS). Also shown is the variation rate for the same period (line). Variation rate = $([(x_1-x_0)/x_0] \times 100)$ where x_1 is the number of publications for that year and x_0 is the number of publications from the preceding year. ALSA = ALS Association.

1982, 1986, and 1995. These years correlate with major milestones for ALS research, clinical practice, and patient advocacy (figure).

We could map major events in ALS research and treatment in the United States by examining the US publication record. In 1982, a focus on ALS cases in Guam provoked numerous articles on the topic, which continued through the next decades. In 1985, the ALS Association (ALSA) was established, which coincides with the second significant rise in the number of publications in 1986. Although the Muscular Dystrophy Association was in existence since 1950, ALSA was the first patient organization formed with a focus exclusively on ALS, and in 1987 the first ALS multidisciplinary clinic opened in the United States. ALSA provides support and promotes improved treatment options, accessibility, and education. Consequently, it has an important impact on ALS research and care. The third spike in publications occurred in 1995, the year the US Food and Drug Administration approved riluzole, which succeeded discovery of the *SOD1* gene in 1993 and publication of the Escorial criteria for the diagnosis of ALS in 1994.

Applying findings to SA. Our analysis of the US publication record suggests that new discoveries and guidelines, drug release, and patient advocacy correlate with more research and, presumably, better implementation of care. The shortage of SA publications disallows a calculation of variation, but small increments in the record were evident after the discovery of a new locus, *ALS8* (8–13 articles), and a Brazilian survey of cases (4–7 articles),[3,5] while the sale of riluzole in 1996 in Brazil and Uruguay had no significant effect.

As demonstrated from the increase in ALS publications after the emergence of ALSA in the United States, the presence of a strong patient organization can encourage publications and better disease treatment. In Brazil and Argentina, where publication output is the highest, there are 2–3 active ALS advocacy groups. In Uruguay, Chile, Colombia, and Peru, ALS patient associations are far less active. ALS patient organizations improve disease visibility and influence physicians, consequently increasing ALS research. Thus, they may help leverage resources in an underdeveloped region and improve both research and ALS patient care.

Based on our data, our expectation is that support of ALS research programs, encouragement of high-quality English-language ALS publications, the formation of vibrant ALS patient advocacy organizations, and the establishment of ALS multidisciplinary clinics can reverse trends of undertreatment and inattention to ALS. Our initiative in Ecuador follows this premise.

Our experience in Ecuador. Ecuador is among the SA countries with no ALS publications, which based on our evidence are the regions with the least care and research resources for ALS. Our project was the first to focus on ALS research in this underdeveloped country.

Adherence to standardized diagnostic criteria increases with training. Therefore, we took several approaches to educate physicians about ALS. We

engaged the support of the Ecuadorian Neurologist Society, prepared Spanish-language guidelines for ALS diagnosis and treatment, organized seminars on ALS EMG, diagnosis, and treatment, and partnered with neurologists from major hospitals. Fifteen medical students from public and private universities volunteered in our research, shadowing US neurologists during patient evaluations and planning and attending seminars. In the area of patient advocacy, we worked with an existing patient organization for multiple sclerosis to sponsor the creation of an ALS patient advocacy group. We also promoted patient education through seminars and literature, and for general public awareness endorsed ALS articles for the media. We believe this has reduced the stigma of a terminal disease and enhanced patient participation in our study. Developing cooperation between research, clinical care, and patient advocacy helped us combine resources for ALS research in an underdeveloped region.

AUTHOR CONTRIBUTIONS

Dr. Bucheli: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content, and study supervision. Calderon: acquisition of data, critical revision of the manuscript for important intellectual content. Chicaiza: acquisition of data, critical revision of the manuscript for important intellectual content. Franco: acquisition of data, critical revision of the manuscript for important intellectual content. Lopez: acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. Digga: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Salameh: critical revision of the manuscript for important intellectual content. Dr. Atassi: critical revision of the manuscript for important intellectual content. Dr. Berry: critical revision of the manuscript for important intellectual content, manuscript revision, supervision.

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