Internal Medicine Review

Multiple Sclerosis: Changing Trends in Latin Americans. Epidemiology and Regional Characteristics.

August 2017

Author
Victor M. Rivera
Baylor College of Medicine
Houston, Texas

Current address:
Victor M. Rivera, MD, FAAN
(Distinguished Emeritus Professor)
3838 N. Braeswood Blvd # 418
Houston, Texas 77025
Email: vrivera@bcm.edu

Abstract

Multiple Sclerosis (MS), a demyelinating autoimmune CNS disorder, affects the susceptible individual through a complex pathogenic process conditioned by interactions between genetics and environmental factors. MS prevalence has remarkably increased in Latin America (LATAM). Historical introduction of the European HLA genetic signature (DRB15) appears to be a determining element in the increasing propensity to the disease in the region. Other postulated contributing factors include accessibility to MRI technology, utilization of modern diagnostic criteria and increasing public awareness. Mestizos, a complex racial group resulting from centuries of admixture between white Caucasians of European origin, Amerindians (Asian/Mongoloid ancestry) and African genetics, constitute the predominant Latin American (LA) ethnic group being affected by MS, while non-mixed Amerindians appear to have an inheritable genetic resistance. Variable frequencies across the region may reflect lack of uniformity of the epidemiologic tools employed. There is no clear north/south gradient MS distribution in LATAM while the proposed theoretical protective role of exposure to Ultraviolet Solar Radiation (UVSR) and vitamin D concentration has not been established in these areas. The only potential environmental agent studied in depth in the region is Varicella-Zoster Virus (VZV) identified as the most prominent risk factor in MS cohorts from Central Mexico. No phenotypic differences with the "western" (Caucasian) forms of MS have been reported from clinical studies in LA. Neuromyelitis Optica (NMO) is the common differential diagnostic challenge in the Americas considering this disorder typically affects non-Caucasian populations. The "Asian" Opticospinal form of MS thought to be a common variant among LA, most likely represented NMO cases. Progress is been made in diagnostic ascertainments. The overall economic burden MS exerts to the health institutions in the Americas has become a realistic challenge to the developing economies in the region. Potential remedial actions are discussed.

Key Words: Multiple Sclerosis, Latin America, Mestizos, Neuromyelitis Optica.

Introduction

Multiple Sclerosis (MS) is a multifactorial disease of the central nervous system (CNS) in which environmental factors interact with the immunological milieu of a genetically susceptible individual. MS is considered the second most common cause of neurological disability in the young adult after head trauma (1). Its complex challenges (from diagnosis to management) constitute a realistic public health concern in Latin America (LATAM), where the disease exerts an enormous socioeconomic burden despite its relatively low prevalence, considering the majority of these countries are emergent economies (2).

The disease is highly prevalent among white Caucasian populations of northern European ancestry and racial groups derived from their genetic admixtures. MS has a distinct geographic distribution being more prominent in the northern and most southern areas of the globe. Its prevalence appears to increase by 0.33/100,000 inhabitants per each degree of latitude away from the equator's line (3, 4). The reason for this tendency is not completely understood. Susceptible genetics affecting peoples living in the high risk areas appears to be a major factor (i.e. populations from Iceland, Scandinavian countries, the British Isles, north and central Europe, Canada, USA, New Zealand and Australia). Other theories suggest as contributing factor decreased exposure to ultraviolet solar radiation (UVSR) in these areas, hence reduction of metabolic vitamin D utilization particlarly in the northern areas of the globe. Insufficient serum vitamin D (25-hydroxyvitamin D) levels have been associated to early conversion to "Clinically Definite MS" and to severity of disease (5). There is also evidence that MS may develop in individuals whose mothers were vitamin deficient during their pre-natal period (6). A link exists between the vitamin D coding genes and the MS propensity human leukocyte (HLA) *DRB1* (7).

Microbial agents particularly viruses of the herpes family (Epstein Barr, Human Herpes Virus-6 or *HHV-6* and Varicella-Zoster) as well as the bacteria Chlamydia pneumoniae, have been proposed as environmental agents acting as *non-self*-antigens in the pathogenesis of MS contributing to the initiation of the erroneous inflammatory autoimmunological cascade that eventually damages the CNS, so characteristic of the disease (8).

Most likely due to the introduction of high risk European genes into diverse world populations MS has become a universal disease affecting groups that were considered naïve to this disorder being transformed at present into susceptible cohorts. A clear example of this historical phenomenon is MS in LATAM. While MS prevalence has globally increased, a documented epidemiological augmentation has also affected the regional frequencies in the tropical countries of this hemisphere. This development is most likely influenced by several factors including utilization of modern criteria for diagnostic ascertainment (9), increasing access to MRI equipment and trained neurologists, and public awareness of a neurological condition that is no longer an exotic disease in the region.

Genetic aspects

The majority of Caucasians with MS (≥66%) carry the genetics haplotype HLA-*DRB*1501-DQA1*0102-DQB1*0602* (DRB15), located in the major histocompatibility complex (MHC) locus in chromosome 6p21-23. This genetic signature is the most common inheritable component in MS but is rare in healthy Asians and Amerindians. MS represents a classic polygenic disease with more than one hundred non-HLA related genes playing a role in this disorder's autoimmunity (10).

The predominant ethnic group among Latin Americans (LA) in the continent is composed by *Mestizos*, a complex population resulting from five centuries of a racial admixture of Caucasian (European), Indigenous or Amerindian (Asian/Mongoloid) and African genetics. The proportion of these components in the peoples from different areas of the Americas is closely attached to social and historic events determining this heterogeneous multiracial fusion. The Mexican genome of its mostly Mestizo population shows a practically similar contribution of Caucasian and Amerindian elements with minimal participation of African genetics (< 3%) (11). Genomewide Association Studies (GWAS) in Mexican Mestizos with MS have shown a distinct enrichment and predominance of European genetics (12). In the other hand, Puerto Rican and Dominicans have the largest proportion of African Ancestry (13). Since HLA-DRB15 has been determined in biracial Brazilian populations (Afro-Brazilians) with MS as well as in Mexican Mestizos with familial MS, the European genetic contribution to the disease among Latin American groups appears to be a determining factor (14). GWAS have not been carried out in other populations in the Americas.

A consistently reported observation throughout the American continent is the lack of documented MS cases in non-mixed ('pure') Amerindians, suggesting a genetic protection or resistance factor owed to their almost total Asian genetic ancestry (15).

Epidemiology

MS prevalence in LATAM continental regions fluctuates from low risk: Bolivia 1.7/100,000 (the lowest); Ecuador 3.2/100,000, to medium: Monterrey, Mexico, 30/100,000 and Buenos Aires, Argentina 38.2/100,000 (the highest) (16, 17). A notable exception is provided by the prevalence in the island of Puerto Rico reportedly to be 68.8/100,000 with an annual incidence of 5.0/100,000 (18). The reason for this disproportionate difference with the continental rates has not been fully explained. There is current data on MS frequencies from practically all countries of LATAM, particularly specific cities or areas, (19, 20, 21) while incidence has been studied in only a few places (Table 1). The prevalence distribution rates do not follow a clear north/south gradient as it is typically seen in the European continent (22). A contributing factor to discrepant epidemiologic data in the Americas is likely related to the lack of uniformity of the methodology employed.

Before MRI technology and validated diagnostic criteria existed, an influential

study in 1970 from Alter and Olivares (23) reported that the prevalence in Mexico was 1.6/100,000, "*one of the lowest in the world*", hence initiating a long-lasting perception that MS was a rare disorder in the Americas. More recent studies indicate a real increase in MS prevalence in LATAM (24, 25). The LA population with MS in the US has been estimated in about 25,000 to 30,000 (26), but these numbers have not been confirmed or properly studied.

In view of the theoretical protective role against MS in populations exposed to high USVR, the tropical countries in LATAM would qualify for this premise but studies from the region confirming the hypothesis are lacking.

The role of microbial agents as antigens initiating the typical inflammatory autoimmune cascade characteristic of MS in a genetically susceptible individual is a recognized composite event (27). This complex reaction involves interaction between the innate and adaptive immune systems. The antigen introduction initiates (among still unknown immune reactions) activation of T-Cells, B-Cells, innumerable molecular pathways, macrophages and microglia, release of pro-inflammatory cytokines and epitope spread. The process eventually damages CNS myelin, axons, oligodendroglia and neurons (28). The possible antigenic role of the environmental bacteria Chlamydia pneumoniae in MS (29) has not been established and studies assessing its theoretical epidemiologic impact in MS in LATAM have not been performed. Some observations on HHV-6 adjudicate its effect to molecular mimicry mechanisms (30). Epstein - Barr virus is the most studied microbe as a possible environmental antigen in the MS setting in Western Europe, USA and Canada (31), but there is no data of its role in LATAM environs. In the other hand, studies in Central Mexico have distinctly identified Varicella-Zoster Virus as the predominant risk factor for MS in this population (32).

Helminth parasitosis in a LA cohort was shown to produce chronic, protective anti-inflammatory immunologic responses with induction of regulatory CD25+, CD4 and FoxP3 cells along with reduction of pro-inflammatory L-12 and Interferon ɣ secreting cells (33). These immunologic reactions appear to favor beneficial clinical and MRI effects. It has been therefore suggested that parasite infection may exert a possible protective effect against MS (34).

Clinical characterizations

MS phenotypes among LA share the same clinical patterns of the Caucasian ("western") type of the disease. The most common presentation is the relapsing/remitting form followed by the secondary progressive and primary progressive types (35).

In LATAM, the main differential diagnosis is posed by Neuromyelitis Optica (NMO) and the other manifestations of its clinical spectrum. This disorder produces prominent involvement of optic nerves and extensive longitudinal cord involvement and may have a relapsing course. NMO affects mostly Asian and non-Caucasian populations; it is characterized by a severe inflammatory demyelinating process resulting of antibody

induction to Aquaporin-4 channels in the CNS, a totally different pathogenesis from MS. While NMO is increasingly being recognized in LATAM, its incidence remains lower comparison to the reportedly current rates of MS frequencies (*NMO/MS ratio = 1:24*),

(36). Advance of knowledge on NMO mechanisms and clinical behavioral features suggests the previously denominated "Asian and Latin American Opticospinal MS Form" is most likely just a variety of the NMO spectrum. Observations among Mexican-Americans with MS show that immigrants reach a higher and earlier level of disability than their counterparts born in the US. Immigrants also appear to have a later onset of disease (37). Whether these clinical behaviors are related to sociopolitical factors inherent to this population in the US affecting their timely and effective health care access rather than representing a real phenotypic variation remains to be established.

Socioeconomic aspects

Access to general MS care and to *Disease Modifying Therapy* (DMT) has gradually become a realistic economic health concern in the Americas, particularly over the last decade in view of the escalating cost of medications. This situation is further confounded by the facts that MS carries a relatively low epidemiologic burden in the region and it is not properly recognized as a significant health issue by the diverse sanitary institutions. Only Paraguay has accomplished the disease to be officially categorized as a "catastrophic illness" assuring access to therapies to all its citizens with MS (38). Similar efforts in Dominican Republic, Guatemala and Mexico, have been initiated. The elevated price of specific DMT medications for MS: injectable interferons and glatiramer acetate, intravenously infused monoclonal antibodies and newer highly effective oral therapeutic molecules, has limited, in addition to other factors, their acquisition by social security and public health institutional formularies. Most countries in LATAM cannot adjudicate funds to study or support conditions like MS which to a certain degree became an unexpected apparition in their public health scenario. Suboptimal utilization of DMT may affect prognosis and disease stability. It is imperative to continue the process of education of health officials and design systems in LATAM to make therapies and general MS management more accessible to patients (39).

Table 1 **Epidemiology of MS in countries and regions in LATAM**

	Prevalence /100³	Incidence /100³
MEXICO (North America)		
•Monterrey	30	
•Chihuahua	14	
•Central Mexico	12	
CENTRAL AMERICA		
Guatemala	≥5.0	
El Salvador		
Honduras		
Nicaragua		
Costa Rica		
Panama	5.24	0.61
CARIBBEAN		
CUBA		
•Cienfuegos	10.0-25.5	
Puerto Rico	68.8	5.0
SOUTH AMERICA		
Venezuela	5.0-10.0	
Colombia	1.5-5.0	
Ecuador	3.2	
Peru	7.6	
Bolivia	1.5	
Paraguay	5.7	
BRAZIL		
•Sao Paulo	15.0	
•Belo Horizonte	18.1	
Chile	5.69	1.81
ARGENTINA		
•Buenos Aires	38.2	1.76
URUGUAY		
•Montevideo	20.5	2.24

Epidemiologic data (references 16-22) includes the entire countries or specific areas (•) from Mexico (Monterrey, Chihuahua, Central Mexico), Cuba (Cienfuegos), Brazil (Sao Paulo, Belo Horizonte), Argentina (Buenos Aires) and Uruguay (Montevideo).

References

1.Noseworthy JH, Luchinetti C, Rodriguez M, et al. Multiple Sclerosis. N Engl J Med 2000; 343 (13): 938-952.

2. Rivera VM. Multiple Sclerosis in Latin America. Reality and Challenge. Neuroepidemiology 2009; 32: 294-295.

3. Compston A. Multiple Sclerosis. The Lancet 2008; 372 (9648): 1502-1517.

4. Abad P, Castro E, Pérez M, et al. Prevalence of Multiple Sclerosis in Ecuador. Neurología 2010; 25 (5): 309-319.

5. Hanwell HE, Reinhold V, Bar-Or A, et al. Serum 25-hydroxyvitamin D status as a determinant of Multiple Sclerosis outcome following an initial demyelinating event in children. Mult Scler 2008; 14: S4.

6. Munger KL, Alvo J, Hongell K, et al. Vitamin D status during pregnancy and risk for multiple sclerosis in offsprings of women in the Finnish Maternnity Cohort. JAMA Neurol 2016; 73 (5): 515- 519.

7. Trowsdale J, Knight JC. Major Histocompatibility Complex Genomics and Human Disease. Annu Rev Genomics Human Genet 2013 (14): 301-323.

8. Bickley S. Infections and MS-What's the evidence? (posted 23 Jun 2014) https://www.mssociety.org.uk (accessed 4 June 2017.

9. Polman C, Reingold S, Banwell B, et al. Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions of the McDonald Criteria. Ann Neurol 2011; 69 (2): 292-302.

10. The International Multiple Sclerosis Genetics Consortium: Risk alleles for multiple sclerosis identified by genomewide study. N Engl J Med 2007; 357: 1-13.

11. Seguin B, Hardy B-J, Singer PA, et al. Genomics public health and developing countries; the case of the Mexican National Institute of Genomic Medicine (INMEGEN). Nat Rev Genet 2008; 9: 56-59.

12. Ordoñez G, Romero S, Orozco L, et al. Genomewide admixture study in Mexican Mestizos with Multiple Sclerosis. Clin Neurol Neurosurg 2015; 130: 55-60.

13. Rivera VM. Prólogo Presidencia LACTRIMS 2001-2005; in Arriagada RC, Nogales Gaete J (eds): Esclerosis Múltiple. Una Mirada Iberoamericana. New York, Demos Medical Publishing, 2008.

14. Alvarado-de la Barrera C, Zúñiga-Ramos J, Ruiz-Morales J, et al. HLA Class II genotypes in Mexican Mestizos with familial and nonfamilial multiple Sclerosis. Neurology 2000; 55 (12): 1897-1900.

15. Flores J, González S, Morales X, et al. Absence of multiple Sclerosis and demyelinating Diseases among Lacandonians, a Pure Amerindian Ethnic Group in Mexico. Multiple Sclerosis International 2012, Article ID 292631, 4 pages, doi: 10.1155/2012/292631.

16. Melcon MO, Melcon CM, Bartoloni E, et al. Towards establishing MS prevalence in Latin America and the Caribbean. Mult Scler 2013; 19: 145-152.

17. Cristiano E, Patrucco L, Miguez D, et al. Increasing prevalence multiple Sclerosis in Buenos Aires, Argentina. Multiple Sclerosis and Related Disorders 2016; 9: 91-94.

18. Chinea A, Rios-Bedoya CF, Rubi C, et al. Incidence of Multiple Sclerosis in Puerto Rico, 2014: A Population-Based Study. Neuroepidemiology 2017; 48 (1-2): 55-60.

19. Gracia F, Castillo LC, Benzadon A, et al. Prevalence and incidence of multiple Sclerosis in Panama (2000-2005). Neuroepidemiology 2009; 32 (4); 287-293.

20. Papais-Alvarenga RM, Vasconcelos CC, Carra A, et al. Central nervous system idiopathic inflammatory demyelinating disorders in South America: A descriptive, multicenter, cross-sectional study. *PLoS One* 2015; 10:e0127757.

21. Lana-Peixoto MA, Frota ERC, Campos GB. The prevalence of multiple Sclerosis in Belo Horizonte, Brazil. Arq Neuro-Psiquiatr 2012; 70: http://dx.doi.org/10.1590/50004-282x201200000006. (accessed 3 July 2017).

22. Melcon MO, Gold L, Carra A, et al. Multiple Sclerosis in the Argentina Patagonia: lack of a latitude gradient. Neurology 2004; 62: A219.

23. Alter M, Olivares L. Multiple Sclerosis in Mexico: an epidemiologic study. Arch Neurol 1970; 23: 455-454.

24. Cristiano E, Patrucco L, Giunta D, et al. Incidence of Multiple Sclerosis in Buenos Aires: a 16 year health maintenance organization-based study. Eur J Neurol 2009; doi: 10.1111/j-1468-1331.2009.02846.

25. Callegaro D, Goldbaum M, Morais L, et al. The prevalence of multiple Sclerosis in the city of Sao Paulo, Brazil. Acta Neurol Scand 2001; 104: 2208-2137.

26. Rivera VM. Multiple Sclerosis in Latin Americans: Genetic Aspects.

Curr Neurol Neurosci Rep 2017; 17:57 DOI 10.1007/s11910-017-0768-4.

27. Hemmer B, Nessler S, Zhou D, et al. Immunopathogenesis and immunotherapy of multiple sclerosis. Nature Clinical Practice Neurology 2006; 2: 201-211.

28. Steinman L. Multiple sclerosis: A coordinated immunological attack against myelin in the central nervous system. Cell 1996; 85: 299-302.

29. Hammerschlag MR, Apfalter P, Boman J, et al. The role of Chlamydia pneumoniae in Multiple Sclerosis: Real or Fictitious. J Infect Dis 2005; 142 (7): 1305-1307.

30. Tejeda-Simon MV, Zang YQ, Hong J, Rivera VM, et al. Cross-reactivity with myelin basic protein and human herpes virus-6 in Multiple Sclerosis. Ann Neurol 2003; 53 (2): 189-197.

31. Tselis A. Epstein-Barr Virus cause of multiple sclerosis. Curr Opin Rheumatol 2012; 24 (4): 424-428.

32. Ordoñez G, Martínez-Palomo A, Corona T, et al. Varicella zoster virus in progressive forms of multiple sclerosis. Clin Neurol Neurosurg 2010; 112 (8): 653-647.

33. Correale J, Farez M. Association between parasite infection and immune responses in multiple sclerosis. Ann Neurol 2007; 61: 97-108.

34. Correale J, Farez MF. Does helminth activation of toll-like receptors modulate immune response in multiple sclerosis patients? Front Cell Infect Microbiol 2012; 2: 112.

35. Rivera VM. II Congreso de LACTRIMS. Rev Neurol 2002; 35 (12): 1175-1176 (Editorial).

36. Cristiano E, Patrucco L, Soriano ER, et al. Incidence and prevalence of Multiple Sclerosis in an HMO in Argentina. Mult Scler 2002; 8: S36.

37. Amezcua L, Lund BT, Weiner LP, et al. Multiple sclerosis in Hispanics: a study of clinical disease expression. Mult Scler 2011; 17 (8): 1010-1016.

38. "Cartes promulga ley de asistencia gratuita a pacientes con esclerosis múltiple" (*Cartes declares law of free assistance to patients with multiple Sclerosis).* Wednesday 31 May, 2017. www.ultimahora.com/ (accessed 3 July 2017).

39. Rivera VM, Macías MA. Access and barriers to MS care in Latin America. Mult Scler J. Experimental Translational Clinical January-March 2017; 1-7 DOI: 10.1177/2055217317700668.