Multiple Sclerosis in the Latino/Hispanic American

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Disclosures

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Hispanic Americans

Objectives:
- Incidence/prevalence in US
- Clinical characteristics
- Asian features
- Migration’s influence
- Vitamin D

Hispanic Americans

- Based on the 2010 U.S. Census Survey
  - 16.3% of population
- Largest Hispanic groups:
  - Mexicans with 67%,
  - followed by Puerto Ricans almost 10%,
  - Cuban 3.5%
  - El Salvador, Dominican and Guatemala (≤3 %)

Projections: 29% by 2050

Hispanics and MS

- Hispanic Whites (HW) are considered to be less susceptible to MS,
- recent reports suggest an increase in MS incidence and prevalence throughout Latin America

While environmental and genetic interactions are involved in MS

Race and ethnicity are likely to play a role in susceptibility and clinical outcome


Racial and ethnic differences in the incidence of MS in US

Golf Era MS Cohort: Blacks were highest at 12.1 (11.2–13.1), Whites at 9.3 (8.9–9.8) and others 6.9 (6.0–7.9).

*For 83 Hispanics defined for 2000–07, the rate was 8.2 (interval 6.5–10.1).

THE PUERTO RICO STUDY FOR THE PREVALENCE OF MULTIPLE SCLEROSIS-

- Puerto Rico is a Caribbean island with a population of 3,994,259 (2007)
- Health Survey 2003/2005, Puerto Rico (PR) has a crude MS prevalence rate of 52/100,000 inhabitants.1

1. PRMSF Epidemiological Study (2009); personal communication and Courtesy of Angel Chinea, MD

Puerto Ricans with MS

In line with what we would expect overall

Age of Onset in Hispanics appears to be younger than non-Hispanic white

Analyzed enrollment data from the Registry of the North American Research Committee on Multiple Sclerosis (NARCOMS) Project to compare 26,967 Caucasians, 715 Latinos, and 1,313 African Americans with MS

<table>
<thead>
<tr>
<th></th>
<th>Hispanics</th>
<th>AA</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS symptom</td>
<td>28.6 years</td>
<td>29.8 years</td>
<td>30.1 years</td>
</tr>
<tr>
<td>MS diagnosis</td>
<td>34.5 years</td>
<td>35.8 years</td>
<td>37.4 years</td>
</tr>
</tbody>
</table>


Age of Onset of MS in Hispanics in Southern California

- USC’s Hispanic Registry
- KP Multiethnic Cohort

Reports from whites *should not* be generalized to Hispanic Americans

Age of Onset in Hispanics younger than non-Hispanic white

University of Miami MS Registry

<table>
<thead>
<tr>
<th></th>
<th>HW (mean ± se.)</th>
<th>NHW (mean ± se.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (years)</td>
<td>33.42 ± 0.62</td>
<td>34.78 ± 0.61</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>37.83 ± 0.67</td>
<td>40.37 ± 0.62</td>
</tr>
<tr>
<td>Diagnostic lag (years)</td>
<td>4.31 ±0.41</td>
<td>5.58 ±0.48</td>
</tr>
</tbody>
</table>

*HW (n=286) appear to be diagnosed earlier than NHW cases (n=276) after adjustment for age at exam (p=0.04).

Clinical Presentation:

**Mexico**: high frequency of optic neuritis as initial symptom (33% compared to historical 14-19% European)\(^1\)

**Southern California**\(^2\)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>HW</th>
<th>NHW</th>
<th>OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optic Neuritis(^a)</td>
<td>31.5</td>
<td>19.7</td>
<td>1.69</td>
<td>0.10</td>
</tr>
<tr>
<td>Sensory(^a)</td>
<td>13.9</td>
<td>27.9</td>
<td>0.41</td>
<td>0.03</td>
</tr>
<tr>
<td>Motor(^a)</td>
<td>13.0</td>
<td>14.7</td>
<td>0.86</td>
<td>0.74</td>
</tr>
<tr>
<td>Transverse Myelitis(^a)</td>
<td>25.0</td>
<td>13.1</td>
<td>2.22</td>
<td>0.07</td>
</tr>
<tr>
<td>Other</td>
<td>16.7</td>
<td>18.0</td>
<td>0.94</td>
<td>0.92</td>
</tr>
</tbody>
</table>

\(^a\) 70% Mexican

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South Florida*- Hispanic Symptoms

<table>
<thead>
<tr>
<th>Location of symptoms at onset</th>
<th>HW (%)</th>
<th>NHW (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Optic Neuritis</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Long Tract Sensory</td>
<td>47</td>
<td>50</td>
</tr>
<tr>
<td>Long Tract Motor</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>32</td>
<td>27</td>
</tr>
<tr>
<td>Cognitive</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

*HW individuals and NHW initially present with similar symptoms.
*Sensory deficits and spinal cord symptoms were the most common MS initial presentation in both groups.

49% Caribbean, followed 12% S. America

Delgado, Silvia, et al. (2013). Comparison of Clinical Disease Expression of Multiple Sclerosis between Hispanics and non-Hispanics patients, poster at AAN 2013
   -courtesy of Dr. Delgado

MS in Latin America

- Preponderance of combined optic nerve and motor Deficits:
  1. Colombia
  2. Brazil
  3. Cuba
  4. Panama
  5. Mexico

- 1: 12.4 MS/OSMS ratio

Admixture in Hispanics

1) Cultural Diversity:

2) Genetic Diversity:

- ancestrally linked Asian, African and Europeans\(^1\)
- Mating pattern:
  Most Hispanics descend from European men and Native American (Asian derived) or African women\(^2\)

**Perception:** Asian Background thought to be protected in MS due to the low incidence/prevalence of MS in Asian countries like Japan and low number of cases in natives

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Ancestral components in Hispanics

**Contrast to AA:**
- African roots of African Americans-
  *uniform mixing* of multiple West African populations
- AA subjects have on average, 16% European and <10% Indigenous American admixture.

**East Coast** Hispanics have higher mean African admixture and
**West Coast** Hispanics have higher mean Indigenous admixture
- Reflection of different continental origins

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1. Johnson et al Ancestral components of admixed genomes in a Mexican cohort. Plos genetics 2011
140 Hispanic cases with MS

2,193 ancestry informative markers that have been previously reported to capture between and within continental heterogeneity. 

Figure 1: Global Ancestry estimated via STRUCTURE. Asian ancestry ranged between 4% to 83% (mean=41)

Absence of Multiple Sclerosis and Demyelinating Diseases among Lacandonians, a Pure Amerindian Ethnic Group in Mexico

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Multiple Sclerosis (MS) is a highly polymorphic disease characterized by different neurologic signs and symptoms. In MS, racial and genetic factors may play an important role in the geographic distribution of this disease. Studies have reported the presence of several protective alleles against the development of autoimmune disorders. In the case of MS, however, they help define MS as a complex disease, and confirm the importance of environmental agents as an independent variable not associated with ethnicity.

A sample of 5,372 (10% of population) 16% parasitized
Spinal Cord in Hispanics with MS-Asian trait?

- Longitudinal SC lesions (LESCLs) reported in 14–31% of Asians with relapsing MS
- LESCLs reported in 1-3% of whites
- we examined the distribution of spinal cord lesions and its relationship with disability in Hispanics


Fig 1: multifocal cord lesions, Fig 2: LESCLs from Amezcua et al.

Presence of LESCLs were associated with the greatest risk to disability (OR 7.3, 95% CIs 1.9–26.5; p = 0.003) compared to no spinal cord lesions independent of disease duration, sex, and age of first symptom.
Ancestry in Hispanics with MS

Figure 1: 45 cases with estimated global ancestry (via the program STRUCTURE).

European ancestry, mean = 48%, Amerindian ancestry ranged between 4% to 83% (mean=41%), African and Asian ancestry had an average estimated proportions of 5% and <1%, respectively. A single individual had a large estimated African ancestry of 73% (Ethnicity: Cuban)

We found that an increasing proportion of non-European ancestry was significantly associated with: an increased risk of LESCLs (p=0.03) and LESCLs were associated with increased disability (p=0.05)

Admixture: Cultural Diversity in Hispanics

• Different Origins despite common language
  – variation exists in diction, speech patterns, vocabulary, and vernacular usage, each unique to a region of origin
  – Social and cultural factors
• May impact:
  • MS progression and its treatments
• Potentially adds a significant barrier


Could admixture in Hispanics facilitate localization of genetic variants important to disability and help us understand the behaviour of the disease?
Age of onset in Hispanics with MS

Migration in MS has been primarily associated with susceptibility and age of onset.\textsuperscript{1-4}

- individuals raised in a region of high MS prevalence, but whose ancestors originate from regions in which MS is rare, have an earlier age of MS onset


Effect of Nativity on Age of onset

<table>
<thead>
<tr>
<th></th>
<th>Migration after age 15 (n = 27)</th>
<th>Born in US or migration before age 15 (n = 43)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of diagnosis</td>
<td>35.7 ± 2.16</td>
<td>35.3 ± 1.42</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age of 1st symptom</td>
<td>34.0 ± 2.31</td>
<td>24.1 ± 1.47</td>
<td>0.0003</td>
</tr>
<tr>
<td>F:M</td>
<td>0.9:1</td>
<td>2:1</td>
<td>0.13</td>
</tr>
<tr>
<td>Age of migration*</td>
<td>26.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median lag from migration to disease onset</td>
<td>14.5 yrs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\*Mean and standard error (SE), **Age of migration available for 2537 (92%).

After adjusting for sex, age of diagnosis and disease duration in this cohort, \textsuperscript{*migrants to the USA after age 15 had more than threefold (OR 3.61, 95% CI 1.1–12.2) increased risk of having ambulatory disability.}

South Florida: Effect of Country of Birth on Age at Onset and Age at Diagnosis in HW

- HW patients born in the USA have a significantly earlier Age at Onset (29.2±0.90) compared to HW patients born outside the USA (35.5±0.78) after adjustment for site of ascertainment (p<0.001)
- HW patients born in the USA have a significantly earlier Age at Diagnosis (31.96±0.95) compared to HW patients born outside the USA (40.75±0.80) after adjustment for site of ascertainment (p<0.001)

Delgado, Silvya, et al. (2013). Comparison of Clinical Disease Expression of Multiple Sclerosis between Hispanics and non-Hispanics patients, poster at AAN 2013

Courtesy from Dr. Delgado

Hispanics and Migration/Immigration

- A complex population of US-born and foreign-born immigrants (Figure)
- Age of immigration and nativity are important social factors related to acculturation. 5,6
- Less is known if migration influences disability. 7,8

Demographics of Hispanics with MS

**Table 1: Baseline characteristics, nativity and age of migration of Hispanics with MS**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>US Born n=202</th>
<th>Early Migrant n=35</th>
<th>Late Migrant n=67</th>
<th>Overall n=304</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n %</td>
<td>132 (65)</td>
<td>19 (54)</td>
<td>38 (57)</td>
<td>189 (62)</td>
<td>0.27</td>
</tr>
<tr>
<td>Relapsing Remitting, n %</td>
<td>169 (84)</td>
<td>30 (86)</td>
<td>61 (81)</td>
<td>260 (82)</td>
<td>0.09</td>
</tr>
<tr>
<td>Age, yrs*</td>
<td>39.1 (11.1)</td>
<td>42.4 (13.0)</td>
<td>44.9 (11.2)</td>
<td>40.8 (11.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age 1st symptom, yrs*</td>
<td>28.5 (9.7)</td>
<td>31.9 (12.9)</td>
<td>34.2 (11.9)</td>
<td>30.1 (10.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age of migration, yrs***</td>
<td>0 (0.0)</td>
<td>6 (3, 12)</td>
<td>22.5 (19, 29)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis, yrs*</td>
<td>30.1 (10.4)</td>
<td>32.5 (13.6)</td>
<td>36.6 (11.1)</td>
<td>31.8 (11.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease duration, yrs*</td>
<td>9.2 (7.5)</td>
<td>9.9 (8.3)</td>
<td>8.4 (7.6)</td>
<td>9.1 (7.5)</td>
<td>0.60</td>
</tr>
<tr>
<td>EDSS of ≥6, n %</td>
<td>37 (18)</td>
<td>3 (0)</td>
<td>19 (28)</td>
<td>68 (19)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Abbreviations: * means and standard deviations, yrs=years, *** Median, interquartile range (Q1, Q3)

Most were of Mexican background, which is consistent with Los Angeles County demographics.1

L. Amezcua et al. Are Recent Immigrants at Higher Risk of Disability with MS? Presented at AAN 2014; oral and manuscript submitted.

http://factfinder2.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=DEC_SF1_QTP3

The association between birth place, migration and disability in relapsing remitting MS (n=280)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Unadjusted OR (95% C.I.)</th>
<th>p-value</th>
<th>Adjusted OR (95% C.I.)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Female)</td>
<td>0.8 (0.42-1.37)</td>
<td>0.36</td>
<td>0.8 (0.41-1.55)</td>
<td>0.50</td>
</tr>
<tr>
<td>Age 1st Symptom (yrs)</td>
<td>1.0 (0.98-1.03)</td>
<td>0.85</td>
<td>1.0 (0.99-1.06)</td>
<td>0.15</td>
</tr>
<tr>
<td>Disease Duration (yrs)</td>
<td>1.1 (1.05-1.14)</td>
<td>&lt;0.0001</td>
<td>1.1 (1.08-1.19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Socioeconomic (County)</td>
<td>1.6 (0.85-3.20)</td>
<td>0.14</td>
<td>1.3 (0.62-2.63)</td>
<td>0.51</td>
</tr>
<tr>
<td>US born</td>
<td>(ref)</td>
<td>(ref)</td>
<td>(ref)</td>
<td>(ref)</td>
</tr>
<tr>
<td>Early-immigrant</td>
<td>0.5 (0.15-1.83)</td>
<td>0.31</td>
<td>0.4 (0.09-1.48)</td>
<td>0.16</td>
</tr>
<tr>
<td>Late-immigrant</td>
<td>2.1 (1.11-4.13)</td>
<td>0.02</td>
<td>2.3 (1.07-4.82)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Only individuals with MS symptoms after age 17 (n=256): Late-immigrants were still found to be at a two fold risk of severe disability (OR 2.0 CI 0.87-4.43, p=0.11) compared to US born.

L. Amezcua et al. Are Recent Immigrants at Higher Risk of Disability with MS? Presented at AAN 2014; oral and manuscript submitted.
Immigration and Risk of Disability

- Higher disability was associated with a later age of immigration to the US.
- While these results could be explained by genetic, ethnic/racial and environmental differences, behavioral and social factors that parallel migration should also be considered. 1-4
- Stress, tobacco use (9% in our sample), and mental health services are reported to be exacerbated in recent immigrants.

Examples of Disparity in Care

Few questionnaire base studies on services:
- Latinos (44%) with MS had more depression compared to whites (39%)
- Latinos never received the various mental health services

- MS management for low-income minorities in New York with 31% of women and 28% of men Hispanic
  - 1/3 never treated by MS specialists

References:


Other potential explanations

- Social: diet changes are strongly tied to assimilation into American culture
- Access to care: most are underinsured/indigent
- Hygiene hypothesis: Immigrants in their country of origin might have been parasitized and now clean in the new country
- Genetic: Gradients of increasing Native American background and of correspondingly decreasing European ancestry have been reported as a function of birth origin from North to South.

Hispanics and Vitamin D - Reflection of cultural practices and genetics?

**Hispanics Practice:**
Use less sunscreen
Outdoor occupations
But yet less in diet – high lactose intolerance, less fish consumption

**Genetic:**
- vitamin D receptor polymorphisms
- Skin- higher melanin production
- GWAS and Vitamin D concentrations in Hispanic Americans without MS
- genetic variability and heritability was found between 25(OH)D and its active metabolite, 1,25-dihydroxyvitamin D$_1$
Environmental: Vitamin D levels in Hispanics with MS

NHANES Report 2005

Season of blood draw and disability level did not influence serum 25(OH)D levels in Hispanics with MS

Amezcua, L, Chung, R, Conti, DV and Langer-Gould, AM. Vitamin D levels in Hispanics with MS. J Neurol 2012 Dec
Summary: Hispanics with MS

1. Lower risk of MS compared to whites but higher risk than Asians
2. Younger age of disease onset compared to whites
3. Birth Place and age of immigration appears to have an effect on age of disease onset and disability
4. Genetic diversity may be responsible for certain clinical and radiological features observed in the disease
5. Social/Cultural diversity may be complicating access to care and utilization
6. Environmental: lower vitamin D than whites—significance in Hispanics with MS still unclear

Last Note

• Ethnicity/Race does play a role in MS
• How do we resolve this?
  – Increase our understanding of subpopulations
    Epidemiological studies
    Clinical trials (increase diversity)
    Collaboration
    Patient Outcomes and integration of social cultural factors
Thank You!

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