Multiple Sclerosis in the Latino/Hispanic American

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Disclosures

• Dr Amezcua has received honoraria for advisory boards from Acorda, Biogen, Questcor, and Novartis.
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• Dr. Amezcua has received consulting honoraria from Teva and Genzyme.
Hispanic Americans

Objectives:
To describe:
- Related incidence/prevalence in US
- Age of onset
- Migration’s influence in disease
- Social Factors
- Vitamin D
- Asian features of the disease

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 suggests 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

<table>
<thead>
<tr>
<th>Table 1: Differences by Gender in Certain Variables among Multiple Sclerosis Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Age of Onset</td>
</tr>
<tr>
<td>22</td>
</tr>
<tr>
<td>Age of Diagnosis</td>
</tr>
<tr>
<td>Interval between Onset and Diagnosis</td>
</tr>
<tr>
<td>Duration of MS</td>
</tr>
</tbody>
</table>

In line with what we would expect overall

Age of Onset of MS in Hispanics in Southern California


Reports from whites should not be generalized to Hispanic Americans


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 in Hispanics appears to be younger than non-Hispanic white

South Florida- University of Miami

<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).

Delgado, Silvya, 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

Age of onset in Hispanics with MS

Migration in MS has been primarily associated with susceptibility and age of onset.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 = 42)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Diagnosis (mean ± SD)*</td>
<td>35.7 ± 2.16</td>
<td>25.5 ± 1.42</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age of 1st symptom (mean ± SD)</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>2.1:1</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 time from migration to disease onset</td>
<td>143 yrs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Mean and standard error (SE), **Age of migration available for 2527 (92%).

After adjusting for sex, age of diagnosis and disease duration in this cohort, 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 (29.21±0.90) compared to HW patients born outside the USA (35.52±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, Silvia, 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)

- Timing of immigration is a proxy to acculturation. 5,6

- Less is known if migration influences disability.7,8


Immigration and Disability in MS

- Population: cross-sectional study of 304 Hispanics with MS from the USC Hispanic MS Registry.

- Hispanic self-identification along with identification of ethnic origin, and verified by a comprehensive, self-administered questionnaire.

- Birth and Immigrant status:
  - US Born
  - early-immigrant (age at immigration <15 years)
  - late-immigrant (age at immigration ≥15 years)

- Risk of disability (expanded disability status scale ≥6) by birth, immigrant status was adjusted for age at symptom onset, sex, and disease duration, using logistic regression

L. Amezcua et al Are Recent Immigrants at Higher Risk of Disability with MS? Presented at AAN 2014; oral and manuscript submitted
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</th>
<th>Early Migrant</th>
<th>Late Migrant</th>
<th>Overall</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 (92)</td>
<td>0.27</td>
</tr>
<tr>
<td>Relapsing Remitting, n %</td>
<td>168 (84)</td>
<td>30 (86)</td>
<td>61 (91)</td>
<td>260 (92)</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>40.6 (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 (1.1)</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 (13.3)</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 (6)</td>
<td>19 (28)</td>
<td>59 (19)</td>
<td>0.04</td>
</tr>
<tr>
<td>Ethnic Origin:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexican</td>
<td>141 (71)</td>
<td>22 (43)</td>
<td>43 (62)</td>
<td>206 (67)</td>
<td>0.11</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.

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 (0.40-1.52)</td>
<td>0.47</td>
</tr>
<tr>
<td>Age 1st Symptom (yrs)</td>
<td>1.0 (0.98-1.03)</td>
<td>0.85</td>
<td>1.0 (0.99-1.20)</td>
<td>0.16</td>
</tr>
<tr>
<td>Disease Duration (yrs)</td>
<td>1.1 (1.05-1.14)</td>
<td>&lt;0.0001</td>
<td>1.1 (1.08-1.20)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>US born (ref)</td>
<td></td>
<td></td>
<td></td>
<td></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=263):

Late-immigrants were still found to be at a two fold risk of severe disability (OR 2.0 CIs 0.89-4.48, p=0.09) 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
- An in-depth assessment of the perceptions and attitudes about MS are warranted in this population.

Data regarding 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

Asian features in Mexican background*

**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>Frequency (%)</th>
<th>Risk for HW compared with NHW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optic Neuritis*</td>
<td>31.5</td>
<td>1.99</td>
</tr>
<tr>
<td>Sensory**</td>
<td>13.9</td>
<td>0.41</td>
</tr>
<tr>
<td>Motor**</td>
<td>13.0</td>
<td>0.86</td>
</tr>
<tr>
<td>Transverse Myelitis*</td>
<td>25.0</td>
<td>2.22</td>
</tr>
<tr>
<td>Other</td>
<td>16.7</td>
<td>0.94</td>
</tr>
</tbody>
</table>

\(\text{OR} = \text{test} / \text{control} \)


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, Silvas, 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
Admixture in Hispanics

1) Cultural Diversity:

2) Genetic Diversity:

- ancestrally linked Asian, African and Europeans¹
- Mating pattern:
  Most Hispanics descend from European men and Native American (Asian derived) or African women²

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


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

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*\(^1\)

![Figure 1: Global Ancestry estimated via STRUCTURE. Asian ancestry ranged between 4% to 83% (mean=41) USC Hispanic MS data- private data not published](image)

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**Spinal Cord in MS**

- LESCLs seen in 14–31 % of Asians with classical MS, while the prevalence in whites is only 1–3 %
- we examined the relationship between spinal cord, OSMS and disability in Hispanics


Fig 1: multifocal cord lesions, Fig 2: LESCLs from Amezcua et al.
Spinal Cord in Hispanics

Presence of LESCLs were associated with the greatest risk to disability (OR 7.3, 95% CI 1.9–26.5; p = 0.003) compared to no spinal cord lesions.

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)

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
• May impact:
  • MS and its treatments
  • Potentially adds a significant barrier to adequate care to begin with

Translation of material is not enough!

Cultural Diversity or Acculturation

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

Hispanics and Vitamin D

**Common practices:**
- Use less sunscreen
- Expect more to be in High sun occupations
- Dietary differences – high lactose intolerance, less fish

**Genetic:**
- Vitamin D receptor polymorphisms
- Skin
- 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

Environmental: Vitamin D levels in Hispanics

NHANES Report 2005

Table 2 Differences in serum 25(OH)D levels between Hispanics and whites with MS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Whites</th>
<th>Hispanics</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entire cohort</strong></td>
<td>κ = 80</td>
<td>κ = 80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>25(OH)D &lt; 30 ng/mL, μ (SD)</td>
<td>37.3 (19.8)</td>
<td>25.1 (9.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>25(OH)D &lt; 20 ng/mL, μ (SD)</td>
<td>33 (41)</td>
<td>26 (70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No vitamin D supplement use</td>
<td>κ = 68</td>
<td>κ = 71</td>
<td></td>
</tr>
<tr>
<td>25(OH)D &lt; 30 ng/mL, μ (SD)</td>
<td>32.1 (13.1)</td>
<td>24.6 (8.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>25(OH)D &lt; 20 ng/mL, μ (SD)</td>
<td>33 (49)</td>
<td>26 (72)</td>
<td>0.005</td>
</tr>
<tr>
<td>25(OH)D &lt; 20 ng/mL, μ (SD) test</td>
<td>12 (10)</td>
<td>26 (37)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Amezcua, L, Chung, R, Conti, DV and Langer-Gould, AM. Vitamin D levels in Hispanics with MS. J Neurol 2012 Dec
Season of blood draw did not influence serum 25(OH)D levels in Hispanics with MS

Amezgua, 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 African Americans and whites
2. Younger age of disease onset compared to whites
3. Nativity appears to have an effect on age of disease onset and disability in Hispanics
4. Genetic diversity may be responsible for certain clinical and radiological features observed in the disease
5. Cultural diversity may be complicating access to care and utilization
6. Environmental: lower vitamin D
Thank You!

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