Trends in primary central nervous system lymphoma incidence and survival in the U.S.

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Primary central nervous system (CNS) lymphoma

- Incidence rate: 7 per million in the U.S.
- Risk increases strongly with immune suppression
  - HIV-infected people: 50-fold increased risk
  - Solid organ transplant recipients: 15-fold increased risk
- Etiology may differ by immune status
  - Most immunocompromised cases are Epstein-Barr virus positive
  - Some suggest that rates of immunocompetent PCNSL are increasing

O’Neill et al., 2013; Gibson et al., 2014; Engels, unpublished data; Chimienti et al., 2009
HIV and PCNSL

- Highly active antiretroviral therapy (HAART) was introduced to treat HIV in 1996
  - PCNSL rates decreased by 60% in the post-HAART era
- Impact of HIV epidemic apparent at the population level
Population-level trends consist of immunocompetent and immunocompromised cases

- National PCNSL trends are highly contaminated by HIV-infected cases (1/4 of cases during 1980-2007).

Shiels et al., JAMA 2011
Approaches used to exclude HIV-infected PCNSL cases

- Excluding populations with higher HIV prevalence
  - San Francisco area residents
  - Never married
  - <65 year-olds
- Exclude deaths due to HIV and other infectious diseases
- Approaches incompletely remove HIV-infected cases and do not address cases among transplant recipients

O’Neill et al., 2013; Olson et al., 2002; Norden et al., 2011
Study Aims

1. To quantify the fraction of PCNSL that occurred among people who are HIV-infected or transplant recipients
2. To estimate trends in immunocompetent PCNSL over time
3. To compare survival after PCNSL diagnosis among HIV-infected and HIV-uninfected cases
Data sources

- General population rates: 10 SEER registries, 1992-2011
  - CNS lymphoma defined based on SEER site recode (NHL) and topography codes C70.0-C72.9.
- HIV-infected cases: classified as HIV-infected if
  - Positive indicator of HIV status recorded at the time of diagnosis (i.e., “HIV flag”). Unknown values were classified as HIV-negative; or
  - HIV recorded as the cause of death (4.5% of unknown/negative HIV flag).
Estimation of PCNSL in transplant recipients

- Transplant-associated cases:
  - Estimated with data from the Transplant Cancer Match Study
    - Record linkage study of the Scientific Registry of Transplant Recipients (SRTR) and cancer registries
  - Calculated IR for transplant-related CNS lymphoma in the TCM Study in strata defined by calendar year, race/ethnicity, sex and age.
    
    \[
    \frac{\text{# of CNS lymphoma cases linked to SRTR}}{\text{Person-years in cancer registries in TCM}}
    \]

- Applied stratum-specific IRs to person-years in SEER -> number of CNS lymphoma cases expected to have occurred among transplant recipients.

- Immunocompetent cases=total-(HIV-infected+transplant)
Characteristics of CNS lymphoma cases in 10 SEER registries, 1992-2011

- 64% B-cell, 1.0% T-cell, 4.8% NHL, unknown lineage and 30.1% NHL, NOS.
- 83.3% occurred in the brain

<table>
<thead>
<tr>
<th></th>
<th>Immunocompetent</th>
<th>HIV-infected</th>
<th>Transplant recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Total</td>
<td>2608</td>
<td>1512</td>
<td>38</td>
</tr>
<tr>
<td>Median age, IQR*</td>
<td>67 (52, 77)</td>
<td>37 (32, 42)</td>
<td>52 (42, 62)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1318 (50.5)</td>
<td>1388 (91.7)</td>
<td>22 (57.9)</td>
</tr>
<tr>
<td>Female</td>
<td>1290 (49.5)</td>
<td>124 (8.2)</td>
<td>16 (42.1)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>1798 (69.0)</td>
<td>778 (51.5)</td>
<td>19 (50.0)</td>
</tr>
<tr>
<td>Other</td>
<td>810 (31.1)</td>
<td>734 (48.5)</td>
<td>19 (50.0)</td>
</tr>
</tbody>
</table>

Shiels et al., Br J Haem 2016
Proportion of total PCNSL cases in HIV+ and transplant populations

<table>
<thead>
<tr>
<th></th>
<th>Total (%)</th>
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<tbody>
<tr>
<td></td>
<td>HIV+</td>
</tr>
<tr>
<td>Males and Females</td>
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</tr>
<tr>
<td>Total</td>
<td>36.4</td>
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<tr>
<td>Males</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>50.9</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>0–19</td>
<td>4.5</td>
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<tr>
<td>20–39</td>
<td>88.5</td>
</tr>
<tr>
<td>40–64</td>
<td>50.6</td>
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<tr>
<td>65+</td>
<td>1.8</td>
</tr>
<tr>
<td>Race/ethnicity</td>
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<tr>
<td>Non-Hispanic white</td>
<td>44.8</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>84.6</td>
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<tr>
<td>Hispanic</td>
<td>63.1</td>
</tr>
<tr>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8.7</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>0–19</td>
<td>5.0</td>
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<td>20–39</td>
<td>54.5</td>
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<td>44.8</td>
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<tr>
<td>Hispanic</td>
<td>12.6</td>
</tr>
</tbody>
</table>

Shiels et al., Br J Haem 2016
Proportion of total PCNSL cases in HIV+ populations

![Bar chart showing HIV prevalence in PCNSL cases for men and women from 1992-1996 to 2007-2011.](chart.png)

- **1992-1996**
  - Men: 70
  - Women: 10

- **1997-2001**
  - Men: 40
  - Women: 10

- **2002-2006**
  - Men: 20
  - Women: 5

- **2007-2011**
  - Men: 10
  - Women: 5

*Shiels et al., Br J Haem 2016*
Age-standardized trends in total and immunocompetent PCNSL

Shiels et al., Br J Haem 2016
Age-standardized trends in total and immunocompetent PCNSL

Incidence rate per 100,000

Men

Women

APC=0.7

APC=0.9

Shiels et al., Br J Haem 2016
Age-standardized trends in total and immunocompetent CNS lymphoma

Men

Incidence rate per 100,000

20-39 years

40-64 years

65+ years

Women

Incidence rate per 100,000

20-39 years

40-64 years

65+ years

APC=-1.2

APC=-0.5

APC=1.7*

APC=N/A

APC=-0.1

APC=1.6*

Shiels et al., Br J Haem 2016
Survival after diagnosis in HIV+ and HIV- cases

1992-2011

- Proportion Alive
- Months after CNS Lymphoma Diagnosis
- 5-year survival
  - HIV+: 8.3%
  - HIV-: 26.2%

1998-2011

- Proportion Alive
- Months after CNS Lymphoma Diagnosis
- 5-year survival
  - HIV+: 14.1%
  - HIV-: 28.9%

Shiels et al., Br J Haem 2016
Changes in 5-year survival in HIV-uninfected cases

- Slight increases in 5-year survival from 20.2% in 1992-1996 to 29.2% in 2002-2006

Shiels et al., Br J Haem 2016
Study Strengths

- SEER population-based data
- Estimates of transplant-associated cases
- Direct assessment of HIV status through HIV flag
Revisiting approaches used by other studies

- Exclusion of higher HIV prevalence populations in SEER
  - San Francisco registry (HIV prevalence in remaining cases: 33%)
  - Never married men and women (13.1%)
  - People aged <65 years old (1.2%)
- Exclusion of people who died from HIV and other infectious and parasitic diseases (8.0%)

Limitations

- Counts of people living with HIV in SEER areas were not available for all years from CDC
  - Denominators of immunocompetent incidence rates included HIV+ people and transplant recipients
  - Rates are slight underestimates
- HIV flag is incomplete (~50%) and has imperfect sensitivity
- We were unable to remove transplant recipients from survival estimates
  - With only 38 expected cases, transplant recipients were unlikely to have influenced survival estimates
- “Immunocompetent” cases include people with other immune conditions
Conclusions

- Rates of CNS lymphoma increased during 1992-2011 among immunocompetent 65+ year-old men and women
  - Does not reflect trends in overall NHL (rates plateaued in 2004).
  - May reflect improved imaging for diagnosis
    - However, glioma rates have remained stable over the same time period
  - May be due to increased immunosuppressive therapies for autoimmune disease among older people
- Despite recent small improvements, survival among both HIV-infected and HIV-uninfected PCNSL cases remain poor.

Olson, Cancer 2002; Shiels, CEBP 2013
Collaborators

- National Cancer Institute
  - Dr. Eric Engels
  - Dr. Ruth Pfeiffer
  - Dr. Lindsay Morton
  - Dr. Elizabeth Yanik

- Cancer registries
  - Dr. Christina Clarke
  - Dr. Leticia Nogueira
  - Dr. Karen Pawlish

- Bicêtre University Hospital
  - Dr. Caroline Besson

- University of Utah
  - Dr. Gita Suneja

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