Does herpes zoster predispose to giant cell arteritis: a geo-epidemiologic study

Purpose: Giant cell arteritis (GCA) is the most common systemic vasculitis in the elderly and can cause irreversible blindness and aortitis. Varicella zoster (VZ), which is potentially preventable by vaccination, has been proposed as a possible immune trigger for GCA, but this is controversial. The incidence of GCA varies widely by country. If VZ virus contributes to the immunopathogenesis of GCA we hypothesized that nations with increased incidence of GCA would also have increased incidence of herpes zoster (HZ). We conducted an ecologic analysis to determine the relationship between the incidence of HZ and GCA in different countries.

Methods: A literature search for the incidence rates (IRs) of GCA and HZ from different countries was conducted. Correlation and linear regression was performed comparing the disease IR of each country for subjects 50 years of age or older.

Results: We found the IR for GCA and HZ from 14 countries. Comparing the IRs for GCA and HZ in 50-year-olds, the Pearson product-moment correlation (r) was −0.51, with linear regression coefficient (β) −2.92 (95% CI −5.41, −0.43; p=0.025) using robust standard errors. Comparing the IRs for GCA and HZ in 70-year-olds, r was −0.40, with β −1.78, which was not statistically significant (95% CI −4.10, 0.53; p=0.12).

Conclusion: Although this geo-epidemiologic study has potential for aggregation and selection biases, there was no positive biologic gradient between the incidence of clinically evident HZ and GCA.

Keywords: epidemiology, shingles, temporal arteritis, immunopathogenesis

Introduction

Giant cell arteritis (GCA) is the most common systemic vasculitis in the elderly and can cause irreversible blindness, myocardial infarction, aortic aneurysm, stroke and rarely death. The incidence of GCA is projected to increase as our population ages, with predicted cost of $76 billion in the United States alone, by the year 2050.

Gilden et al and Nagel et al found varicella zoster virus (VZV) in the temporal arteries of 73% of patients with biopsy-proven GCA and propose VZV as a possible trigger in the immunopathogenesis of GCA. Although this potential role of VZV in the development of GCA has not been substantiated by other investigators, and remains controversial, Gilden suggested adjunctive antivirals be considered in the treatment of GCA.

The incidence rate (IR) of GCA varies widely by country, being the highest in northern Europe and lowest in Asia. We hypothesized that if VZV contributed to GCA, the GCA IRs per 100,000 subjects, 50 years of age or older (IR_{GCA}) per country should correlate with the local herpes zoster IRs (IR_{HZ}). To test this hypothesis, we performed a regression analysis using the published IR_{GCA} and IR_{HZ} from different countries.
Methods

The IR\textsubscript{GCA} was searched for on PubMed, Embase, and Google Scholar from inception to July 1, 2017 using the search terms: incidence, epidemiology, country, temporal arteritis and GCA. The same search was repeated using herpes zoster and shingles in place of the arteritis terms.

The country specific IRs for subjects 50 years of age and older were recorded per 100,000 population for GCA, and per 1,000 person-years for HZ. If IRs were provided for multiple years, the results were averaged (Table 1).

The IR\textsubscript{GCA} in Japan was calculated using Koboyashi’s reported prevalence rate of 1.47 per 100,000 in subjects aged 50 years or older, with average age of onset of 71.5 years.\textsuperscript{7} Lifespan is thought not to be affected by GCA unless the patient has aortic aneurysm or dissection.\textsuperscript{8} The average life expectancy in Japan is 83.3 years.\textsuperscript{9} As GCA is a rare disease and recurrent, the IR was estimated as the prevalence rate/duration of disease = 1.3 per million subjects 50 years or older.

Since the peak onset of GCA is in the 8th decade,\textsuperscript{10} we also examined the IR of HZ in 70 year-olds. If the age brackets straddled our chosen age cut-offs, the IR values from the two adjacent brackets were averaged.

Only countries/regions that had IRs available for both GCA and HZ were used for analysis. Paired t-test was used to examine the time difference in year of publication between the GCA and HZ studies for each country. There was inadequate information in the GCA articles to consistently calculate the within-study standard errors needed for meta-regression. Pearson product-moment correlation coefficients, and linear regression with and without robust standard errors was performed. White’s test was used to test for heteroscedasticity. All statistical tests were conducted with Stata 14.2 (StataCorp LP, College Station, TX, USA), and a two-sided \( p<0.05 \) was considered statistically significant.

Results

The IRs for both GCA and HZ were available for 14 countries (Table 1), and plotted on Figure 1. With the exception of Olmsted County and the United Kingdom, the availability of IR\textsubscript{GCA} and IR\textsubscript{HZ} from the same time frame and corresponding geographic region was limited. Eight of the 14 countries (57%) in Table 1 were overlapping in the time frame of the corresponding GCA and HZ studies. On paired t-test, the GCA studies were published on average 4.5 years before the HZ studies \((p=0.09)\). A published IR\textsubscript{GCA} for Iceland was available. The IR\textsubscript{HZ} for Iceland was only available for the 60-year age group only \((4.7 \text{ per 1,000})\), but not the 50-year-old or 70-year-old age groups, and as such was not used.

Pearson product-moment correlation coefficient \((r)\) comparing IR\textsubscript{GCA} with: IR\textsubscript{HZ} in 50-year-olds was \(-0.51 \text{ (} p=0.07)\), and IR\textsubscript{HZ} in 70-year-olds was \(-0.40 \text{ (} p=0.16)\). Linear regression with robust standard errors showed a regression coefficient \((\beta)\) \(-2.92 (95\% CI \text{ -5.41, -0.43; } p=0.025)\) between the IR\textsubscript{GCA} \(\geq 50\)-year-olds, and the IR\textsubscript{HZ} in 50-year-olds. For the IR\textsubscript{HZ} in 70-year-olds, no statistically significant linear dependence of the mean IR\textsubscript{GCA} on IR\textsubscript{HZ} was detected \((\beta= -1.78, 95\% CI \text{ -4.10, 0.53; } p=0.12)\). White’s test did not suggest heteroscedasticity (Table 2).

Table 1 Incidence rates of giant cell arteritis and herpes zoster per country

<table>
<thead>
<tr>
<th>Country</th>
<th>GCA study: year published (study period/region)</th>
<th>IR\textsubscript{GCA}</th>
<th>HZ study: year/region</th>
<th>IR\textsubscript{HZ50}</th>
<th>IR\textsubscript{HZ70}</th>
<th>Time overlap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norway, B+C\textsuperscript{27}</td>
<td>2014 (2006–2012)/South</td>
<td>21</td>
<td>2016 (2008–2012)/National\textsuperscript{38}</td>
<td>2.8</td>
<td>7.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Finland, B+C\textsuperscript{30}</td>
<td>1992 (1984–1988)/West Nyland</td>
<td>26.2</td>
<td>2010 (2000–2006)/Tuusula, Kangasala, Salo\textsuperscript{40}</td>
<td>2.5</td>
<td>6.5</td>
<td>No</td>
</tr>
<tr>
<td>Sweden, B\textsuperscript{41}</td>
<td>2015 (1997–2010)/Skane</td>
<td>14.1</td>
<td>2013 (2006–2010)/National\textsuperscript{42}</td>
<td>2.5</td>
<td>8.0</td>
<td>Yes</td>
</tr>
<tr>
<td>United Kingdom, B+C\textsuperscript{43}</td>
<td>2006 (1990–2001)/National</td>
<td>22</td>
<td>2003 (1991–2000)/National\textsuperscript{44}</td>
<td>4.0</td>
<td>9.3</td>
<td>Yes</td>
</tr>
<tr>
<td>USA, C\textsuperscript{45}</td>
<td>2015 (2000–2009)/Olmsted City</td>
<td>19.8</td>
<td>2016 (1945–2007)/Olmsted City\textsuperscript{46}</td>
<td>4.5</td>
<td>8.4</td>
<td>Yes</td>
</tr>
<tr>
<td>New Zealand, B\textsuperscript{49}</td>
<td>2011 (1996–2005)/Otago</td>
<td>12.73</td>
<td>2014 (2009–2013)/Lower Hutt\textsuperscript{50}</td>
<td>6.1</td>
<td>7.3</td>
<td>No</td>
</tr>
<tr>
<td>Israel, B+C\textsuperscript{51}</td>
<td>2007 (1980–2004)/Jerusalem</td>
<td>11.3</td>
<td>2013 (2006–2010)/Tel Aviv\textsuperscript{52}</td>
<td>5.8</td>
<td>11.8</td>
<td>No</td>
</tr>
<tr>
<td>Canada, B\textsuperscript{53}</td>
<td>2007 (1998–2003)/Saskatoon</td>
<td>9.4</td>
<td>2011 (1992–2010)/Ontario\textsuperscript{54}</td>
<td>3.7</td>
<td>7.4</td>
<td>Yes</td>
</tr>
<tr>
<td>France, B+C\textsuperscript{55}</td>
<td>1982 (1970–1979)/Loire-Atlantique</td>
<td>9.4</td>
<td>2010 (2005–2007)/National\textsuperscript{56}</td>
<td>4.2</td>
<td>8.7</td>
<td>No</td>
</tr>
<tr>
<td>Italy, B+C\textsuperscript{57}</td>
<td>2017 (1986–2012)/Reggio Emilia</td>
<td>5.8</td>
<td>2010 (2003–2005)/National\textsuperscript{58}</td>
<td>3.6</td>
<td>7.7</td>
<td>Yes</td>
</tr>
<tr>
<td>Australia, B\textsuperscript{59}</td>
<td>2013 (1992–2011)/Adelaide</td>
<td>3.2</td>
<td>2008 (1998–2006)/National\textsuperscript{59}</td>
<td>6.5</td>
<td>11.5</td>
<td>Yes</td>
</tr>
<tr>
<td>Japan, C\textsuperscript{61}</td>
<td>2003 (1998)/National</td>
<td>0.13</td>
<td>2009 (1997–2006)/Miyazaki\textsuperscript{63}</td>
<td>3.9</td>
<td>7.4</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Notes: B, biopsy proven; C, clinical criteria for diagnosis; Cal, calculated from published prevalence rate; Time overlap, the incidence rates for GCA and HZ were from the same time period.

Abbreviations: GCA, giant cell arteritis; IR, incidence rate; IR\textsubscript{GCA}, giant cell arteritis incidence rates per 100,000 subjects, 50 years of age or older; HZ, herpes zoster; IR\textsubscript{HZ50}, herpes zoster incidence rates in 50-year-old subjects per 1,000 person years; IR\textsubscript{HZ70}, herpes zoster incidence rates in 70-year-old subjects per 1,000 person years.
This ecologic study does not support a positive biologic gradient between the IR\textsubscript{HZ} and IR\textsubscript{GCA}. Subgroup regression analyses of the per country IR\textsubscript{GCA} and IR\textsubscript{HZ}, with and without overlapping timeframes were not statistically significant and did not show a positive regression coefficient.

**Discussion**

Infections can predispose to systemic vasculitis by mechanisms such as molecular mimicry, epitope spreading, immune response to subdominant epitopes normally hidden from T-cell recognition, or bystander activation.\(^{11}\) If there is a causal relationship between HZ and GCA it is important to define since HZ can be potentially prevented with the shingles vaccine, and because the treatment of GCA might benefit from adjunctive antivirals.

VZV and GCA have some overlapping features. Dendritic cells are thought to play a central role in VZV infection and the immunopathogenesis of GCA.\(^{12-14}\) HZ ophthalmicus or multifocal VZV vasculopathy with temporal artery infection may mimic the presentation of GCA. Varicella zoster vasculopathy and GCA can both cause optic neuropathy, cranial nerve palsy, and stroke.

Temporal artery biopsy studies have shown conflicting results on the association of VZV and GCA. Gilden et al and Nagel et al suggested that VZV triggers the immunopathology of GCA, and found increase of 74% VZV in temporal artery biopsy specimens from patients with GCA.\(^{3-5,15}\) However, with the exception of Mitchell and Font,\(^{16}\) other investigators have not found substantial VZV in the arterial specimens of biopsy-proven GCA or clinically diagnosed GCA.\(^{17-22}\) False positive immunohistochemistry from antibody cross-reactivity to shared epitopes between VZV proteins and arterial smooth muscle elements suggest caution when interpreting pathology findings.\(^{23}\) Gilden and Nagel acknowledge

**Table 2** Correlation and linear regression of the incidence rates of giant cell arteritis versus herpes zoster

<table>
<thead>
<tr>
<th>Zoster incidence rate age groups</th>
<th>Number of countries</th>
<th>Correlation coefficient</th>
<th>Regression coefficient</th>
<th>p-value, R(^2)</th>
<th>p-value with robust SE</th>
<th>p-value for white's test</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-year-olds, all countries</td>
<td>14</td>
<td>-0.51</td>
<td>-2.92</td>
<td>p=0.07, R(^2)=0.26</td>
<td>p=0.025</td>
<td>p=0.28</td>
</tr>
<tr>
<td>70-year-olds, all countries</td>
<td>14</td>
<td>-0.40</td>
<td>-1.78</td>
<td>p=0.16, R(^2)=0.16</td>
<td>p=0.12</td>
<td>p=0.42</td>
</tr>
<tr>
<td>50-year-olds, time overlap</td>
<td>8</td>
<td>-0.38</td>
<td>-2.66</td>
<td>p=0.35, R(^2)=0.14</td>
<td>p=0.06</td>
<td>p=0.12</td>
</tr>
<tr>
<td>70-year-olds, time overlap</td>
<td>8</td>
<td>-0.15</td>
<td>-0.88</td>
<td>p=0.72, R(^2)=0.02</td>
<td>p=0.69</td>
<td>p=0.88</td>
</tr>
<tr>
<td>50-year-olds, no overlap</td>
<td>6</td>
<td>-0.80</td>
<td>-4.24</td>
<td>p=0.06, R(^2)=0.63</td>
<td>p=0.05</td>
<td>p=0.93</td>
</tr>
<tr>
<td>70-year-olds, no overlap</td>
<td>6</td>
<td>-0.74</td>
<td>-2.63</td>
<td>p=0.09, R(^2)=0.54</td>
<td>p=0.14</td>
<td>p=0.09</td>
</tr>
</tbody>
</table>

**Notes:** Correlation coefficient, Pearson product-moment correlation coefficient (r); regression coefficient, linear regression coefficient; time overlap, the incidence rates for GCA and HZ were from the same time period; no overlap, the incidence rates for GCA and HZ were from different time periods.

**Abbreviations:** GCA, giant cell arteritis; HZ, herpes zoster; SE, standard error.
that “the presence of VZV in about 20% of temporal artery biopsies from non-GCA post-mortem controls also suggests that VZV alone is not sufficient to produce disease”.5

A population-based cohort study did not find an increased risk of HZ in patients with GCA compared to non-GCA subjects, even during the first 6 months after glucocorticoid initiation, when patients are on the highest doses.24 A large nested case control study determined that HZ had a modest incidence rate ratio of 1.17 in association with incident GCA.25 A review of two large administrative databases found a two-fold increased risk of GCA with complicated HZ.26

Our ecologic study did not show a positive biologic gradient between the IRHZ and IRGCA. Limitations of this study include possible ecologic fallacy, time, location and/or selection biases, the limited availability of IRGCA and IRHZ and variable trends in IR. By and large the IRHZ are increasing.27 Zoster sine herpete and asymptomatic VZV infection may have affected our analysis. The IRGCA may be increasing, decreasing, or cyclical.28 Furthermore, the IRGCA are higher when cases of clinically diagnosed GCA are included with biopsy-proven GCA. It is unlikely that the IRHZ in Table 1 were significantly affected by zoster vaccination. The Oka/Merck zoster vaccine decreases the risk of shingles by only 51%,29 and was approved for use in the United States and European Union in 2006,30,31 and in Canada in 2008.32 The Olmsted county HZ study published in 2016 reviewed two sets of patients, the latest of which were from 1980 to 2007. In the United States a 5% random sample of Medicare seniors were first offered zoster vaccine in 2007, and uptake was low at 3.9%.33 The first two European countries to recommend nation-wide zoster vaccination for seniors 65 to 74 years of age were the United Kingdom and France in 2013.34 The Australian and Ontario, Canada immunization programs for seniors began in 2016.35,36

Conclusion
The discordant IRs for HZ and GCA question the biologic plausibility of clinically overt HZ as the sole immunopathogenic trigger for GCA. Geo-epidemiology may help elucidate the relationship between VZV and GCA, but more widely available, accurate and updated IRs from different countries are required.

Disclosure
The authors report no conflicts of interest in this work.

References


