Increased Risk of Multiple Sclerosis Following Herpes Zoster: A Nationwide, Population-Based Study

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(See the editorial commentary by Corona and Flores, on pages 177–8.)

Objective. Varicella zoster virus (VZV) has been proposed to be involved in the pathogenesis of multiple sclerosis (MS). However, the epidemiological data regarding the MS occurrence rate following herpes zoster are still scanty. The goal of this study is to investigate the frequency and risk for MS following occurrence of herpes zoster.

Methods. This study used the Taiwan National Health Insurance Research Database. A total of 315,550 patients with herpes zoster were included as the study group, and the control group consisted of 946,650 randomly selected subjects. The stratified Cox proportional hazard regression was performed to calculate the 1-year MS-free survival rate.

Results. Of 1,262,200 sampled patients, 29 from the study group (.009%) and 24 from the control group (.003%) had MS during the 1-year follow-up period. After adjusting for monthly income and geographic region, the hazard of MS was 3.96 times greater (95% CI = 2.22–7.07, p < 0.001) for the study group than controls.

Conclusions. Our findings support the notion that occurrence of MS could be associated with herpes zoster attack. We found a significantly higher risk for MS within 1 year of herpes zoster attack compared with the control population.

Multiple sclerosis (MS) is a neurological disease which is caused by autoimmune-mediated demyelination of the central nervous system [1]. The viral hypothesis as triggering MS has been proposed in the body of previous literature [1–4]. The Herpesviridae family, including herpes simplex virus (HSV), varicella zoster virus (VZV), human herpes virus 6 (HHV-6), Epstein-Barr virus, and cytomegalovirus are potential candidates associated with MS [2, 5–7]. Herpes virus is more frequently observed in the demyelination plaque of MS than in normal neuronal tissue [7].

One characteristic of VZV is its ability to become latent in the dorsal root ganglion after primary infection [8]. Herpes zoster, caused by reactivation of VZV, typically manifests as painful skin eruptions over 1–3 dermatomes and is not an uncommon disease. It is considered that immunological derangement, particularly depressed cell–mediated immunity, could play an important role in reactivation of VZV [9, 10]. Although herpes zoster is generally considered a self-limiting condition, it can result in several potential problems, such as long-term neuralgia and blindness [8]. Serious neurological complications such as stroke, encephalitis, vasculopathy, and Guillain-Barré syndrome have been also reported [11–13]. Although the suspicion of the association between MS and herpes zoster has been proposed for some decades, most available epidemiological data have come from retrospective cohorts of MS patients [5, 14, 15]. Marrie et al conducted a systemic review of the association between VZV infection and MS and found insufficient evidence to conclude there is a linkage between the 2 diseases [16, 17].
As MS has low frequency, it is difficult to conduct a large cohort study to clarify this issue. To date, the exact frequency and risk for MS after herpes zoster in the general population remain unknown. From a public health point of view, it is also difficult to estimate the potential impact of herpes zoster on the course of this serious disease, MS. It should be possible to answer this question with a large representative population. Our goal is thus to establish an epidemiological profile regarding the frequency of MS occurrence following herpes zoster attack, through a nationwide, case-control study.

METHODS

Database
This study used the National Health Insurance Research Database (NHIRD) derived from the Taiwan National Health Insurance (NHI) program and maintained by the National Health Research Institutes. As of 2007, 22.60 million of Taiwan’s 22.96 million people were enrolled in this program, amounting to 98.4% of the island’s population. NHIRD provides a registry of contracted medical facilities, a registry of board-certified physicians, and a registry for catastrophically ill patients, plus monthly claim summaries for inpatient claims, monthly claim summaries for ambulatory care claims, and details of inpatient and ambulatory care orders. Hundreds of researchers have published studies based on data from NHIRD.

Since the dataset consists of deidentified secondary data released to the public for research purposes, the study was exempt from full review by the institutional review board of Taipei Medical University.

Study Sample
The study design included a study group and a control group. First, we identified 349,477 patients who had visited ambulatory care centers with a principal diagnosis of herpes zoster (ICD-9-CM code 053) between 1 January 2003 and 31 December 2005. In order to limit our study sample to the adult population, we only selected patients older than 18 years (n = 316,776). In addition, in order to increase the likelihood of selecting only new cases, we excluded patients who had been diagnosed with herpes zoster prior to the year 2003 (1996–2002; since the NHI program was initiated in Taiwan in 1995, we could not trace use of medical services before 1996) (n = 1,028). We assigned their first ambulatory care visits for the treatment of herpes zoster as the index ambulatory care visit. We also excluded patients who had been diagnosed with MS (ICD-9-CM code 340) or any associated systemic diseases such as human immunodeficiency virus (HIV), systemic lupus erythematosus, or lymphoma between 1996 and the index ambulatory care visit (n = 198). Ultimately, 315,550 patients with herpes zoster were included in the study group.

The control group was likewise extracted from the NHIRD. We first excluded those patients who had been diagnosed with herpes zoster or any associated systemic diseases such as HIV, systemic lupus erythematosus, or lymphoma between 1996 and 2006. We then randomly selected 946,650 individuals (3 for every herpes zoster patient) matched with the study group in terms of age, gender, and the year of index ambulatory care visit using the SAS proc surveymatch program (SAS software for Windows, version 8.2). We assigned their first ambulatory care visit occurring in the index year as the index ambulatory care visit. We did not include patients who were under age 18 in their index year or who had MS prior to their index ambulatory care visits. Each patient was then tracked for 1 year from their index visit to identify patients who subsequently developed MS.

Statistical Analysis
The SAS statistical package (version 8.2) was used to perform all statistical analyses. Pearson $\chi^2$ and t tests were done to examine the sociodemographic differences between patients in the study group and control group. The log-rank test was used to examine the difference in the risk of MS between patients with and without herpes zoster. Furthermore, we performed stratified Cox proportional hazard regression (stratified by age, gender, and the year of index visit) to calculate the 1-year MS-free survival rate, after adjusting for patients’ monthly income and the geographical location of the community in which the patient resided (northern, central, eastern, or southern Taiwan). We selected NTS$15,840 as the first income level cutoff point, since this amount is the government-stipulated minimum wage for full-time employees in Taiwan. Significance was set at 2-tailed $P \leq .05$.

RESULTS

Table 1 shows the distribution of demographic characteristics for patients with and without herpes zoster. The mean age was 51.1 years (SD, 17.8 years) for the total 1,262,200 sampled patients; 51.6 and 50.9 for patients with and without herpes zoster, respectively ($P < .001$). After matching for gender, age, and the year of index visit, patients with herpes zoster were more likely to have higher monthly incomes ($P < .001$) and to reside in the northern part of Taiwan ($P < .001$) compared with patients in the control group.

Table 2 presents the distribution of MS between patients with and without herpes zoster. Of the sample of 1,262,200 patients, 53 patients (.004%) were diagnosed with MS during the 1-year follow-up period; 29 from the study group (.009%) and 24 from the control group (.003%) ($P < .001$). Similarly, the log-rank test also suggests that patients with herpes zoster had significantly lower 1-year MS-free survival rates compared with patients without herpes zoster ($P < .001$). The mean MS-free survival time was 104 and 83 days for patients with and without herpes zoster, respectively.
Table 1. Demographic Characteristics of Herpes Zoster Patients in Taiwan and Control Group, 2003–2005 (n = 1,262,200)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with herpes zoster (n = 315,550)</th>
<th>Comparison patients (n = 946,650)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Male</td>
<td>165,073</td>
<td>495,219</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>150,477</td>
<td>451,431</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>18–44</td>
<td>108,341</td>
<td>325,023</td>
<td></td>
</tr>
<tr>
<td>45–64</td>
<td>122,413</td>
<td>367,239</td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>84,796</td>
<td>254,388</td>
<td></td>
</tr>
<tr>
<td>Index year</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>2003</td>
<td>100,493</td>
<td>301,479</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>105,953</td>
<td>317,859</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>109,104</td>
<td>327,312</td>
<td></td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Northern</td>
<td>156,802</td>
<td>443,473</td>
<td>46.9</td>
</tr>
<tr>
<td>Central</td>
<td>59,208</td>
<td>169,860</td>
<td>17.9</td>
</tr>
<tr>
<td>Southern</td>
<td>91,723</td>
<td>288,879</td>
<td>30.5</td>
</tr>
<tr>
<td>Eastern</td>
<td>7817</td>
<td>44,438</td>
<td>4.7</td>
</tr>
<tr>
<td>Monthly income</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NT$1–15,840</td>
<td>48,635</td>
<td>387,909</td>
<td>41.0</td>
</tr>
<tr>
<td>NT$15,841–25,000</td>
<td>147,486</td>
<td>346,776</td>
<td>36.6</td>
</tr>
<tr>
<td>≥NT$25,001</td>
<td>119,429</td>
<td>211,965</td>
<td>22.4</td>
</tr>
</tbody>
</table>

Table 2 also presents the crude and adjusted hazard ratios (HR) for MS between patients with and without herpes zoster. Cox proportional hazard regression (stratified by age, gender, and the year of index visit) reveals that the hazard ratio of MS during the 1-year follow-up period for patients with herpes zoster was 3.63 (95% CI, 2.11–6.23; P < .001) compared to patients without this condition. In addition, after adjusting for monthly income and geographic region, the risk of developing MS during the 1-year follow-up period was 3.96 times greater (95% CI, 2.22–7.07; P < .001) for patients with herpes zoster than for those in the control group.

DISCUSSION

We found that the frequency of MS in the year following herpes zoster attack is .009% in Taiwan. The risk of developing MS among patients with herpes zoster was 3.63-fold greater than that of the matched controls. This is the first study to demonstrate the frequency and risk for MS after herpes zoster through a nationwide, population-based analysis. Our findings provide fundamental data to estimate the potential impact of herpes zoster on the occurrence of MS. Current available data regarding the association between VZV and MS were mostly obtained

Table 2. Crude Hazard Ratios for Multiple Sclerosis Among the Sampled Patients During the 1-Year Follow-up Starting From the Index Ambulatory Care Visit (n = 1,262,200)

<table>
<thead>
<tr>
<th>Presence of Multiple Sclerosis</th>
<th>Total sample</th>
<th>Comparison</th>
<th>Herpes zoster</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
</tr>
<tr>
<td>1-year follow-up period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>53 .004</td>
<td>24 .003</td>
<td>29 .009</td>
</tr>
<tr>
<td>No</td>
<td>1,262,147</td>
<td>946,626</td>
<td>315,521</td>
</tr>
<tr>
<td>Crude HRa (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>1.00</td>
<td>3.63c (2.11–6.23)</td>
</tr>
<tr>
<td>Adjusted HRb (95% CI)</td>
<td></td>
<td>1.00</td>
<td>3.96c (2.22–7.07)</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval; HR, hazard ratio.

a Crude HR was calculated by stratified Cox proportional hazard regression (stratified by age, gender, and year of index visit).
b Adjustment for monthly income and geographic region.
c P < .001.
from Western populations [5, 14–16]. Mixed results have been reported. Several factors should be considered as possible explanations. First, the heterogeneity of results may reflect differences in underlying methodology and design. Since the number of control cases is arbitrary, a relative risk cannot be determined. In addition, recall bias could occur when retrospectively pursuing a patient’s history of herpes zoster. Second, the ethnic and geographic distribution of MS varies across countries [1]. Also, the prevalence of VZV infection varies by different region. These factors could further explain the heterogeneity of results in the current literature.

Although we found that the risk for MS in patients with herpes zoster is increased compared with that of controls, the frequency of MS following herpes zoster is still low. However, from a public health point of view, the overall burden of herpes zoster–associated MS should not be overlooked. It is worth noting that herpes zoster has been suggested to be an emerging health threat, since the prevalence rate increases as the population of elderly and immunocompromised patients in modern society increases [18]. The frequency of herpes zoster may be as high as 1.3–1.6 per 1000 people per year, and cumulative lifetime incidence is about 1–5 per 1000 people per year [19, 20]. Furthermore, MS is a severe neurological disease that is often associated with long-term disability [1, 21]. The economic costs and burden of care associated with MS are quite high. [22]

Our study supports the association between herpes zoster and MS. However, the pathomechanism by which herpes zoster is associated with MS is still unknown. Although it is still controversial, studies show that VZV could be directly involved in the pathogenesis of MS [14, 23–26]. Evidence for a close relationship between the sequential herpetic viral load during remission and relapsing courses of MS has been presented [2, 27]. Furthermore, a few case reports have shown that the invasion of VZV to the central nervous system could result in demyelination-like lesions [28]. Another explanation of the association with MS is that it relates to perturbation of the host’s immunological status, which also triggered the herpes zoster attack. It is still difficult to distinguish which of the 2 phenomena are applicable from current available data. More possibly, both factors could play roles in the association we observed. Interestingly, we found that the mean time from herpes zoster attack to occurrence of MS was 104 days. It has been observed that the latency from an infectious episode to the occurrence of Guillain-Barré syndrome is about 6 weeks; however, data regarding the latency from infectious episodes to occurrence of MS are still lacking. The mechanisms behind the association between herpes zoster and MS may be highly complex and could involve both viral and host factors.

One of the most interesting and important issues is whether we can reduce the likelihood of MS following a herpes zoster attack. Currently 2 important clinical strategies are available for managing VZV infection: prevention through vaccination and treatment with antiviral medications [29, 30]. It has been demonstrated that live attenuated zoster vaccine can reduce the burden of illness of herpes zoster, the incidence of herpes zoster, and postherpetic neuralgia in the elderly [30]. However, it is still not known if the protective effects extend to other age groups. In addition, there should be further investigation about whether the zoster vaccine can provide protection against MS occurrence. Antiviral medications for herpes zoster are usually prescribed for patients, including immunocompromised patients, who have a high risk of developing serious complications (eg, herpes zoster ophthalmicus) [8, 29]. Studies also suggest that antiviral medications could decrease the severity of a herpes zoster attack [8]. However, there are limited data to show whether antiviral medications can reduce the risk of neurological complications. A pilot study used acyclovir to treat MS. Further research is needed to investigate the protective effects against MS of these approaches.

Our study has some advantages: We minimized selection bias by nationwide sampling and used a large representative population and case-control design to provide sufficient statistical power. Nevertheless, several limitations should be addressed. First, the validity of diagnosis and coding of MS in the nationwide registry may be criticized. However, the NHI program conducts a regular cross-checking system with full review of chart records, laboratory findings, and image results by clinical specialists to prevent miscoding or inaccurate medical claims. Furthermore, previous epidemiological studies exploring MS prevalence in Taiwan using the NIHRD compared with hospital-based data yielded a general consistent result [31, 32]. Therefore, we believe that the quality of our database is adequate to analyze the epidemiological profile. Second, some patients with herpes zoster might be missed in our database if they did not seek medical help, particularly when their symptoms were mild. Misestimation of the risk and frequency from our study could occur. However, in our experience, utilization of medical service in Taiwan is generally high because access to medical services is convenient and there is a high coverage rate of insurance. Under this scenario the bias should be low. Third, some variables cannot be determined in our database such as family history, environmental exposure, nutritional status, cigarette smoking, and physical activities. Some of these factors have been suggested to be associated with MS [16]. Finally, the ethnic population of our study is almost entirely Han Chinese. Previous epidemiological data from Taiwan show that the low prevalence of MS is similar to that of other Asian countries, which is lower than in Western population [32]. There may be difficulty extrapolating the results of our study to other ethnic groups.

CONCLUSIONS

Our findings suggest that the occurrence of MS could be associated with herpes zoster attack. We found a significantly higher
risk for MS for patients in the year following a herpes zoster attack compared with the control population. Further study is recommended to explore the mechanisms of this association and potential intervention strategies for prevention.

Acknowledgments

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References