

# Family History as a Risk Factor for Herpes Zoster

## A Case-Control Study

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**Objective:** To assess risk factors for herpes zoster beyond age and immunosuppression, especially the association with a family history of herpes zoster, since a preventative herpes zoster and postherpetic neuralgia vaccine is now available.

**Design:** We undertook a case-control study of herpes zoster, which represents reactivation of latent varicella zoster virus residing in dorsal root ganglia following primary infection, involving 504 patients and 523 controls. Interviews were conducted by trained medical investigators using a structured questionnaire.

**Setting:** The Center for Clinical Studies, an outpatient clinic and research center in Houston, Texas.

**Participants:** Nonimmunocompromised patients with confirmed cases of herpes zoster were included in the

study. Controls were nonimmunocompromised clinic patients with new diagnoses of skin diseases other than herpes zoster.

**Results:** Cases were more likely to report blood relatives with a history of zoster (39%) compared with controls (11%;  $P < .001$ ). Risk was increased with multiple blood relatives (odds ratio, 13.77; 95% confidence interval, 5.85-32.39) compared with single blood relatives (odds ratio, 4.50; 95% confidence interval, 3.15-6.41).

**Conclusions:** The results suggest an association between herpes zoster and family history of zoster. Future studies will be needed to investigate this association.

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**H**ERPES ZOSTER (HZ) REPRESENTS reactivation of latent varicella zoster virus (VZV) residing in dorsal root ganglia following primary infection. While most adults are seropositive for VZV, there is a 10% to 30% lifetime risk of HZ,<sup>1</sup> which approaches 50% for those living to age 85 years.<sup>2</sup> Herpes zoster carries considerable morbidity (postherpetic neuralgia)<sup>3</sup> and substantial health care provider cost.<sup>4</sup> Depressed cell-mediated immunity, increased age, illness, and immunosuppressive therapies increase the risk of HZ. Other associated risks have not been fully elucidated, but sex, ethnicity, seasonality, psychological stress, mechanical trauma, and heavy metal exposure have all been proposed.<sup>1</sup> Recently, the possibility of a genetic susceptibility to zoster has been shown by examining polymorphisms at the promoter region of the gene for interleukin 10, a cytokine known to down-regulate cell-mediated immunity.<sup>5</sup> Patients with HZ carried a higher proportion

(53%) of the ATA haplotype at the promoter region compared with controls (38%).

Similarly, many infectious diseases associated with decreased immunity have been shown to have genetic susceptibility. Several recent reviews have discussed HLA association and genetic susceptibility among diseases such as human immunodeficiency virus (HIV), tuberculosis, leprosy, prions, malaria, and travelers' diarrhea.<sup>6-10</sup> In particular, it has been suggested that HIV 1 susceptibility is associated with the presence of C-protein-coupled 7-transmembrane coreceptors such as CCR5 and CCR2 and suppressive chemokines such as CCL3L1.<sup>11</sup> HLA-B27, known to predispose to rheumatologic diseases, has also been associated with susceptibility to HIV infection and disease progression, as well as the influenza herpes simplex type 2 and Epstein-Barr viruses.<sup>12</sup> Genetic association with these HLA types and chemokines has encouraged researchers to investigate vaccines and tailored treatments for susceptible individuals.

1. Have you been diagnosed with or are you currently undergoing therapy for cancer?
2. Are you infected with HIV/AIDS?
3. Have you ever used or are you currently using any immune-suppressing drugs such as steroids or chemotherapy agents?
4. Have you ever been told by a physician that your immune system or your body's defenses are weakened?

**Figure 1.** Questionnaire to exclude immunocompromised participants. HIV indicates human immunodeficiency virus.

1. Do you currently have a painful, red, linear, and blistering rash or have you ever had one similar to this description before?
2. Have you ever seen a physician due to a painful red, linear, and blistering skin rash that lasted at least 7 to 10 days?
3. Do you have any scars on your body from a painful red, linear, and blistering skin rash that lasted at least 7 to 10 days?
4. Have you ever received therapy for a painful red, linear, and blistering skin rash?
5. If so, did these therapies include valacyclovir hydrochloride (Valtrex), acyclovir (Zovirax), and famciclovir (Famvir)?
  - If they answered "no" to all of questions 1 through 5, they were asked about family history as in Figure 3.
  - If participants answered "yes" to any of questions 1 through 5, they were asked the following questions.
6. Approximately what month and day did you have this rash?
7. How long was it after you noticed the rash before you saw a physician?
8. In the months before your rash outbreak, do you remember any stressful life events such as a move, a divorce, or a death in the family?
9. Where was the rash located on your body?
10. Has this rash come back or did you only have it once?

**Figure 2.** Questionnaire to elicit herpes zoster history. Valtrex, Zovirax, and Famvir are manufactured by SmithKlineBeecham, Research Triangle Park, North Carolina.

1. Do any of your blood relatives currently have shingles or have a history of shingles?
2. If so, how is that person related to you?
3. Did the relative see a physician about their shingles?
4. Did they describe the rash as a painful red, linear, and blistering skin rash that lasted at least 7 to 10 days?
5. Did they describe any scars on their body from this painful red, linear, and blistering skin rash that lasted at least 7 to 10 days?
6. Did they ever describe receiving therapy for the painful red, linear, and blistering skin rash?
7. If so, did these therapies include valacyclovir hydrochloride (Valtrex), acyclovir (Zovirax), and famciclovir (Famvir)?

**Figure 3.** Questionnaire for family history. Valtrex, Zovirax, and Famvir are manufactured by SmithKlineBeecham, Research Triangle Park, North Carolina.

However, a recent review of the literature demonstrated that the association of HZ with family history of zoster has not been adequately evaluated.<sup>1</sup> The goal of the present study was to assess the association of HZ with clinical characteristics beyond age and immunosuppression, focusing on family history as a risk factor. Family history and possible genetic markers could be used to encourage at-risk individuals to be vaccinated, thus reducing morbidity and health care expenditures for the complications of HZ. Furthermore, those at-risk individuals who choose not to be vaccinated could at least be educated regarding the signs and symptoms of HZ.

## METHODS

### SELECTION OF CASE PATIENTS

A case-control analysis was undertaken at the Center for Clinical Studies in Houston, Texas. The patients with confirmed HZ were examined and treated between January 1, 1992, and Au-

gust 15, 2005. As documented in their medical records, patients were all diagnosed by staff dermatologists and thus were only selected for the study if they had a confirmed diagnosis of HZ. All patients who were available and gave informed consent were included in the study. Patients gave voluntary informed consent and were interviewed by medically trained and blinded investigators different from the staff dermatologists who initially diagnosed their HZ and documented their histories. The study was reviewed and obtained institutional review board approval from the University of Texas Health Science Center at Houston. Patients were excluded from the study if they were considered immunocompromised by asking the questions in **Figure 1**.

### SELECTION OF CONTROL SUBJECTS

To exclude factors that would affect the study sample, such as sample distortion bias, controls were chosen among current patients and past nonimmunocompromised patients from the same center as the case patients. These controls included current or past patients with other minor skin conditions as well as patients with chronic skin conditions (eg, psoriasis and atopic dermatitis) who were enrolled in current or prior trials between 1992 and 2005. Controls were chosen from among current or past patients because they would be likely to seek treatment at the center if they were affected with HZ and were thus similar in representation to the cases. The selected controls were age, sex, and race matched by different investigators than those conducting the blinded standardized questionnaire. Control patients were excluded if they were considered immunocompromised by asking the questions in Figure 1.

### DATA COLLECTION

All patients and control subjects selected gave verbal informed consent and voluntarily participated in a standardized telephone interview. Two medically trained investigators, distinct from the investigator in charge of the medical records and data collection, gave the standardized interview. Thus, these 2 investigators were blinded in regard to cases and controls by having the initial investigator sort and screen the case and control groups. They were also blinded to the importance of specific questions for the purpose of the study. Investigators were fully trained in regard to the exact order of the interview questions and how to avoid leading questions. A standardized questionnaire with the same memory stimulation techniques was used to reduce information bias.

Both cases and controls were asked a series of questions to later verify what was already present in the written records and to obtain demographic data such as name, age, sex, race/ethnicity, and memory of primary varicella zoster infection. Because prior studies have suggested race as a possible risk factor for HZ, race/ethnicity was classified both by individuals participating in the study and by the investigators.<sup>1</sup> Participants were not asked about a history of HZ vaccination (zoster vaccine live [Oka/Merck] [Zostavax]; Merck & Co Inc, Whitehouse Station, New Jersey) because our data collection was completed before Zostavax was licensed in May 2006.<sup>13</sup>

Next, participants were asked questions to elicit a potential HZ history. This information would be used during data processing to verify the medical records of the cases and to exclude controls that had recently developed any cutaneous eruptions suggestive of shingles. Participants were asked the series of questions listed in **Figure 2**. If the participants answered yes to any of questions 1 through 5 in Figure 2, they were asked a series of further questions for HZ epidemiologic purposes. All participants were then asked about potential family history using the questions listed in **Figure 3**. For the purposes

**Table 1. Distribution of Cases and Controls According to Age, Sex, and Ethnicity**

Characteristic	Case Patients, No. (%)	Controls, No. (%)	Wald $\chi^2$ (df)	P Value	Adjusted Odds Ratio (95% Confidence Interval)
Age, y			1.97 (7)	.16	1.05 (0.98-1.13)
<25	33 (6.6)	31 (5.9)			
26-35	24 (4.8)	56 (10.7)			
36-45	60 (11.9)	67 (12.8)			
46-55	104 (20.6)	109 (20.8)			
56-65	100 (19.8)	94 (18.0)			
66-75	119 (23.6)	83 (15.9)			
76-85	55 (10.9)	57 (10.9)			
>86	9 (1.8)	26 (5.0)			
Sex			0.00 (1)	.98	1.00 (0.78-1.13)
Male	204 (40.5)	212 (40.5)			
Female	300 (59.5)	311 (59.5)			
Race			4.46 (2)	.10	
White (non-Hispanic)	354 (70.2)	388 (74.2)			White vs African American, 0.91 (0.55-1.51)
Hispanic	52 (10.3)	84 (16.1)			White vs Hispanic, 0.71 (0.48-1.04)
African American	33 (6.6)	33 (6.3)			Hispanic vs African American, 0.62 (0.34-1.12)
Other <sup>a</sup>	65 (12.9)	18 (3.4)			Not included in analysis

<sup>a</sup>Not included owing to statistically inadequate number of individuals for analysis ( $n < 30$ ).

of this study, participants were told that blood relatives included parents, siblings, children, grandparents, aunts, uncles, and first cousins only. Step-relatives and adopted relatives were excluded. Blood relatives with a history of HZ were excluded if they were considered immunocompromised by asking the questions listed in Figure 1.

All data obtained from the interview questions were recorded in database files and error checked with the medical records for quality assurance measures and reliability. Before performing a database analysis and statistical calculation, all controls who answered yes to any of the HZ-specific questions were excluded from the study. They were not reclassified as cases because their suspected HZ could not be confirmed. Both cases and controls who refused to participate were recorded to calculate a participation rate for the study.

### STATISTICAL ANALYSIS

The continuous variables were reported as mean (SD) and were analyzed using the unpaired 2-tailed *t* test. The discrete variables were analyzed using the  $\chi^2$  test. The degree of likeness between cases and controls was assessed using Wald  $\chi^2$  tests. For each variable, including sex, age, race, and family history, we computed the odds ratios (ORs) and corresponding 95% confidence intervals (CIs). In a logistic regression model, age, sex, and race were adjusted for, while total number of relatives with a history of HZ was used as a predictor of HZ. Statistical analyses were performed with SAS version 9.1.3 software (SAS Institute Inc, Cary, North Carolina).

## RESULTS

### PARTICIPANT CHARACTERISTICS

From the active database of 1114 people, 504 well-documented cases and 523 controls were included in the final study. Of the 540 cases and 574 controls who were contacted, only 8 cases (1.5%) and 12 potential controls (2.1%) refused to participate. Response rates were therefore determined to be 98.5% among cases and 97.9%

among controls. Of the controls, 8 (1.4%) were excluded because of potential HZ infection or history, and 31 controls (5.4%) and 28 cases (5.2%) were excluded because of an immunocompromised status. Furthermore, 15 (5.3%) of the cases' blood relatives and 4 (6.2%) of the controls' blood relatives were excluded because of an immunocompromised status. Cases had a mean (SD) age of onset of 57 (17.5) years (range, 8-95 years). Of the cases, 354 were white (70.2%), 52 were Hispanic (10.3%), 33 were African American (6.6%), and 65 were listed as other (12.9%). Other included individuals such as Asians and Native Americans. Among the cases, 67.0% of female vs 55.9% of male patients visited a physician within 72 hours of the onset of a cutaneous eruption ( $P = .01$ ). Female participants were significantly more likely to report a stressful event prior to developing HZ ( $P < .05$ ). No seasonal predilection for HZ was identified. Among the cases, 384 (76.2%) had a memory of primary infection with varicella zoster. Among controls, 402 (76.9%) had a memory of primary infection with varicella zoster. No information about HZ vaccination was obtained in either cases or controls. Involved dermatomic areas included the following: thoracic (263 cases [52.2%]), trigeminal (116 cases [23.0%]), cervical (70 cases [13.9%]), lumbar (44 cases [8.7%]), and sacral (15 cases [2.9%]) regions. Four cases had considerable involvement at 2 dermatomic areas. Of the cases, 42 (8.3%) had clinically and laboratory-diagnosed recurrent HZ (ie, not due to herpes simplex virus). A similar dermatomal distribution was seen across all age, sex, and ethnic groups.

### COMPARISON OF CASES VS CONTROLS

The distribution of case patients and controls according to age, sex, and race is reported in **Table 1**. No differences in age, sex, and race were found between cases and controls. The category of "other" in Table 1 includes individuals who classified themselves as Asian

**Table 2. Distribution of Cases and Controls According to Family History**

Family History	Case Patients, No. (%)	Controls, No. (%)	Wald $\chi^2$ (df)	P Value	Odds Ratio (95% Confidence Interval)
First-degree relatives <sup>a</sup>			73.42 (1)	<.001	4.35 (3.11-6.09)
0	343 (68.1)	482 (92.2)			
1	130 (25.8)	37 (7.1)			
2	28 (5.6)	4 (0.8)			
3	2 (0.4)	0			
4	0	0			
5	1 (0.2)	0			
Non-first-degree relatives <sup>a</sup>			25.75 (1)	<.001	4.27 (2.44-7.49)
0	444 (88.1)	508 (97.1)			
1	52 (10.3)	15 (2.9)			
2	7 (1.4)	0			
3	0	0			
4	1 (0.2)	0			
Total relatives <sup>a</sup>			90.13 (1)	<.001	4.09 (3.06-5.47)
0	306 (60.7)	468 (89.5)			
1	144 (28.6)	49 (9.4)			
2	43 (8.5)	6 (1.2)			
3	9 (1.8)	0			
4	0	0			
5	2 (0.4)	0			
Single vs multiple relatives <sup>a</sup>			98.66 (2)	<.001	
0	306 (60.7)	468 (89.5)			
1	144 (28.6)	49 (9.4)			4.50 (3.15-6.41)
≥2	54 (10.7)	6 (1.2)			13.77 (5.85-32.39)

<sup>a</sup>Numbers for each variable represent the number of blood relatives with a reported history of herpes zoster.

and Native American. These individuals were grouped together because their individual groups were numerically inadequate for statistical analysis (n < 30 per group).

In **Table 2**, we report the distribution of cases and controls according to family history of HZ. A significantly higher proportion of cases reported having a family history of HZ (39.3% vs 10.5%;  $P < .001$ ). Participant status (ie, cases or controls) reliably predicted the reporting of HZ in first-degree relatives (Wald  $\chi^2 = 73.42$ ;  $P < .001$ ), non-first-degree relatives (Wald  $\chi^2 = 25.75$ ;  $P < .001$ ), and total relatives (Wald  $\chi^2 = 90.13$ ;  $P < .001$ ). Cases were 4.35-times more likely than controls to report first-degree relatives with a history of HZ (95% CI, 3.11-6.09). In regard to non-first-degree blood relatives, cases were 4.27-times more likely than controls to have a non-first-degree blood relative with a history of HZ (95% CI, 2.44-7.49). The odds ratio for total affected relatives (both first degree and other) was 4.09 when comparing cases and controls (95% CI, 3.06-5.47). An OR of 4.50 (95% CI, 3.15-6.41) was calculated for those reporting single relatives, and an OR of 13.77 (95% CI, 5.85-32.39) was calculated for those reporting multiple relatives, suggesting a dose-dependent effect.

In the final part of our analysis, we used a logistic regression model in which sex, age, race, and total number of relatives were all used as variables for the prediction of HZ. In this model, sex, age, and race were statistically insignificant predictors of HZ. Total number of relatives with a history of HZ was the only significant predictor of HZ when all other variables were held constant (OR, 3.95; 95% CI, 2.93-5.32) ( $P < .05$ ).

#### COMMENT

The known major risk factors for HZ are increasing age and presence of cell-mediated immunosuppressive disorders such as HIV or AIDS and cancer. A recent review of the literature revealed that the clinical association between HZ and positive family history has not been adequately investigated, but it has been suggested.<sup>1,5</sup>

However, in a recent study investigating genetic susceptibility to HZ, a significant proportion of cases carried the ATA haplotype at the promoter region of the gene for interleukin 10.<sup>5</sup> Ultimately, the role of interleukin 10 is complex, showing both immunostimulatory and immunosuppressive functions, and is not fully understood. The same haplotype has been found to be protective in Epstein-Barr virus infection and other infectious diseases.<sup>14</sup> In light of the genetic advances in infectious disease susceptibility, our study indicates the possibility of inherited susceptibility to HZ and indicates that further studies into this area may be necessary in order to recognize and vaccinate susceptible individuals.

Genetic susceptibility or resistance has also been proposed on the basis of HLA alleles in other viral and infectious diseases including leprosy, prions, malaria, tuberculosis, hepatitis virus, and HIV.<sup>6-10,15</sup> Although HLA alleles have not been extensively studied as a potential source of inherited susceptibility in HZ, a study of post-herpetic neuralgia indicated that HLA class I alleles may indeed control the immune response against VZV and therefore the pathogenesis of postherpetic neuralgia.<sup>16</sup> In a recent study of herpes simplex virus and neuralgia, pa-

tients with certain haplotypes and low levels of IgG3 and IgG1 were found to have more frequent recurrences than controls and other patients with herpes simplex virus ( $P = .04$ ).<sup>17</sup> The fact that most infectious and dermatologic diseases have been associated with HLA types, interleukin polymorphisms, and other genetic characteristics suggests that HZ may also have an inherited susceptibility.

Although not much data exist about family history and HZ, other risk factors beyond immunosuppression and age have been previously studied. For example, in many studies, women appear to have an increased incidence, and therefore risk, of zoster.<sup>18,19</sup> As our study suggests, women may be more likely to initially seek medical advice for their HZ, thereby appearing to have an increased incidence in studies that only allowed enrollment within the first 72 hours of lesion onset. However, the significance of this sex difference is unclear. Thomas and Hall<sup>1</sup> discussed how an increased incidence in women is unlikely given the greater likelihood of social contacts with children compared with men, a well-documented protective factor.<sup>20</sup> This is supported by studies that showed a lower incidence of HZ in women aged 35 to 44 years, but some authors argue that the protective benefits of child contact could be offsetting any increased risk due to other factors. However, Lerman et al<sup>21</sup> evaluated VZV antibody positivity among health care and day care workers as well as blue-collar workers (controls) and found no significant difference in VZV antibody positivity among cases and controls. Furthermore, many studies have shown a decreased incidence of HZ among African Americans later in life compared with whites.<sup>22,23</sup> Although our study found no differences in HZ among the different races, our study involved predominantly white patients, and therefore no assumptions about racial differences in HZ susceptibility can be made based on our data. In regard to age differences in HZ, a recent review has demonstrated that most cases of HZ involve patients 50 years and older.<sup>1</sup> Our study confirms this epidemiologic data, since approximately 75% of cases were in this age range.

Several biases may have affected our results. First, recall bias is inherent to any study in which subjects are asked to recall events that may have occurred many years before. Also, case patients are more likely to recall having had relatives with a family history of HZ because they are more motivated, having had the disease themselves. This could lead to an underestimate of the role of positive family history among controls, who would be less aware of relatives with a history of HZ. However, in our study, both cases and controls were administered identical questionnaires and memory aids to determine whether their relatives had a history of HZ. Second, detection bias exists in any case-control study in which controls are not adequately assessed for the disease. However, we tried to reduce this bias in our study by asking specific questions. These specific questions, listed in Figures 1 through 3, were asked to determine the likelihood of previous or current HZ infection. Based on prior research, clinical diagnosis and questioning have a high degree of accuracy in determining HZ infection and are significantly associated with a positive confirmation by

polymerase chain reaction ( $P < .05$ ).<sup>24,25</sup> Furthermore, to distribute information bias in a nondifferential way for our cases and controls, we used a standardized questionnaire, specifically trained and blinded medical investigators, and standardized methods to stimulate memory. Confounding bias should be reduced based on the inclusion and exclusion criteria stated in the "Methods" section. Last, the strength of the association found in this study between HZ and family history suggests that bias does not completely explain our results. Our study documented a dose-dependent effect between having a single blood relative and having multiple blood relatives with a history of HZ.

With the promising results of the Oka/Merck VZV vaccine study and the new preventive HZ and postherpetic neuralgia vaccine now available for the general public,<sup>26</sup> as well as a vast amount of evidence that infectious and dermatologic diseases have genetic associations, it is important to consider the possibility of inherited susceptibility. Our study suggests a strong association between the development of HZ and having a blood relative with a history of zoster. Since July 2005, we have seen and interviewed 282 additional patients with HZ at their time of diagnosis. In support of our original study, family history of HZ was reported in 49.2% of these additional patients. Such patients represent a population that may be at increased risk of developing HZ and therefore have a greater need for vaccination. Therefore, targeting these at-risk individuals based on their family history may decrease both their chance of future HZ infection and health care expenditures toward HZ morbidity. It remains unclear whether this association is the result of recall bias or whether it reflects inherited susceptibility. Future studies to investigate the role of HLA alleles in HZ cases as well as additional prospective cohort studies to confirm our results are needed.

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**Author Contributions:** Dr Mendoza, a clinical epidemiologist, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Ms Hicks and Dr Cook-Norris contributed equally to the study and the manuscript. *Study concept and design:* Hicks, Cook-Norris, Mendoza, Arora, and Tyring. *Acquisition of data:* Hicks, Cook-Norris, Madkan, and Tyring. *Analysis and interpretation of data:* Hicks, Cook-Norris, Mendoza, Madkan, Arora, and Tyring. *Drafting of the manuscript:* Hicks, Cook-Norris, Mendoza, and Tyring. *Critical revision of the manuscript for important intellectual content:* Hicks, Mendoza, Madkan, Arora, and Tyring. *Statistical analysis:* Mendoza. *Administrative, technical, and material support:* Hicks, Madkan, Arora, and Tyring. *Study supervision:* Hicks, Mendoza, Madkan, and Tyring.

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