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No Evidence of Family History as a Risk Factor for Herpes Zoster in Patients with Post-Herpetic Neuralgia

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Little is known about reactivation of latent varicella zoster virus as herpes zoster in individuals with no underlying immunosuppression. Risk factors include age, sex, ethnicity, exogenous boosting of immunity from varicella contacts, underlying cell-mediated immune disorders, mechanical trauma, psychological stress, and immunotoxin exposure. An association between herpes zoster and family history of zoster has been proposed. A case-control study involving patients affected by post-herpetic neuralgia, which usually follows more severe acute herpes zoster, was performed. The patients with post-herpetic neuralgia were enrolled at the Pain Clinic of the Policlinico Tor Vergata in Rome, Italy, within 1 year from the onset of acute zoster. The controls matched for sex and age were chosen among healthy subjects without a history of herpes zoster presenting at the Internal Medicine Outpatient Clinic for hypertension in the same time period. All the participants in the study gave informed consent and were interviewed by medically trained and blinded investigators using a questionnaire. Similar proportions of the patients and the controls reported a family history of herpes zoster irrespective of the degree of relationship, i.e., 17.4% and 18.2%, respectively, by analyzing only the first-degree relatives [RR 1.03 (CI 95%: 0.78–1.37)], and 28.4% and 29.6%, respectively, by analyzing the total number of relatives [RR 1.03 (CI 95%: 0.81–1.31)]. Further and larger prospective cohort studies are needed to ascertain whether a family history of herpes zoster is really an independent predictor of zoster in different geographical settings. ***J. Med. Virol. 82:1007–1011, 2010.***

KEY WORDS: VZV; herpes zoster; post-herpetic neuralgia

INTRODUCTION

Herpes zoster or "shingles" results from the reactivation of latent varicella zoster virus from the dorsal root and some cranial nerve ganglia. Although herpes zoster is not a reportable disease, an estimated 200,000–250,000 cases occur annually in Italy [di Luzio Paparatti et al., 1999]. The most notable manifestations of shingles in immunocompetent persons are acute neuralgia (pain occurring within 30 days of the onset of the rush) and persistent pain, traditionally termed post-herpetic neuralgia. It is known that post-herpetic neuralgia can persist, in some individuals, for weeks, months, or even years after the herpes zoster rash has healed, causing suffering for the patient and a burden of economic cost on patient, care-givers, and healthcare providers. Because the effect of herpes zoster treatment is disappointing once the disease has developed and a vaccine can reduce its incidence and severity [Oxman et al., 2005], it is important to know which factors predict the occurrence of herpes zoster. The risk factors identified in analytical studies include age, sex, ethnicity, genetic susceptibility, exogenous boosting of immunity from varicella contacts, underlying cell-mediated immune disorders, mechanical trauma, psychological stress, and immunotoxin exposure [Schmader et al., 1990; Thomas and Hall, 2004]. An association between herpes zoster and family history of zoster has been proposed [Ozawa et al., 1999; Haanpaa et al., 2002; Hicks et al., 2008]. A genetic susceptibility to

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a number of infections including herpes encephalitis, which is caused by a virus sharing many similarities with varicella zoster virus, has been reported recently [Casrouge et al., 2006].

The aim of the present study was to examine the possibility that a family history of zoster represents a risk factor for zoster development, since, if confirmed, this could represent a further reason to encourage zoster immunization among the patients' relatives. To this end patients with post-herpetic neuralgia, that usually follows more severe acute herpes zoster, were studied.

METHODS

Selection of the Case Patients and the Control Subjects

A case-control analysis was undertaken at the Policlinico Tor Vergata, Rome, Italy. The patients with post-herpetic neuralgia [defined as pain $\geq$3 on a scale ranging from 0 ("no pain") to 10 ("pain as bad as you can imagine") $\geq$12 weeks after the onset of acute zoster] were enrolled at the Pain Clinic and examined and treated between January 1, 2007, and October 15, 2008, within 1 year from the onset of acute zoster. All the patients who were available and gave voluntary informed consent were included in the study. They were interviewed by medically trained and blinded investigators using a questionnaire. The controls were chosen among healthy subjects without a history of herpes zoster, presenting at the Internal Medicine Outpatient Clinic for hypertension in the same time period. They were age and sex matched by the same investigators conducting the blinded standardized questionnaire with the herpes zoster patients. The study was reviewed and approval was obtained from an institutional review board and the Ethical Committee of the University of Rome "Tor Vergata."

Data Collection

A standardized questionnaire was used during the interviews of the participants in the study (data not shown). In detail, both the patients and the controls were asked a series of questions to obtain demographic data such as name, age, sex, race/ethnicity, and to verify whether they had memory of primary varicella zoster infection. The participants in the study were not asked about a history of herpes zoster vaccination because our data collection was completed before the commercialization of a zoster vaccine in Italy.

The patients as well as the controls were excluded from the study if they were considered immunocompromised by asking questions about the possibility they were infected with HIV/AIDS, they had been diagnosed with cancer and/or they were undergoing treatments with immunosuppressive drugs such as steroids or chemotherapeutic agents.

The participants in the study were also asked a series of questions, which were aimed at obtaining the following information: medical history (diabetes or other underlying diseases), herpes zoster history (number of episodes, presence of a prodrome, intensity of pain, distribution of manifestations, clinical expression of disease, and antiviral treatments), and occurrence of mechanical trauma or stressful events during the last 3 months prior to the onset of herpes zoster or the interview, in the patients and controls, respectively.

Finally, all the participants in the study were asked about a potential family history of herpes zoster. For the purposes of this study, they were told that blood relatives included parents, siblings, children, grandparents, parents' siblings, and first cousins only. Step-relatives and adopted relatives were excluded. Blood relatives with a history of herpes zoster were excluded if they were considered immunocompromised by asking the above-reported questions. All the data obtained from the interviews were recorded in database files.

Statistical Analysis

The variables were analyzed using the chi-square test. For sex and age, the relative risk (RR) and corresponding 95% confidence intervals (CIs) were calculated. The analyses were performed using EPI Info^{TM} version 3.5.1.

RESULTS

One hundred seventy-three well-documented cases of post-herpetic neuralgia and 176 controls were included in the study. All the patients as well as the controls were white Caucasian Italians. The distribution of the patients and the controls according to age and sex is reported in Table I. The patients had a mean (SD) age of onset of 72.4 (12.4) years (range, 22–102 years) whereas the controls of 71.4 (11.9) years (range, 21–92 years) and the median age was 75 years for the case patients and 73 for the controls.

The analysis of the two distributions of age revealed very similar characteristics, hence the variable "age" was coded and the patients classified as belonging to four classes, i.e., under 65, from 65 to 74, from 75 to 84, and equal or over 85 years, respectively.

Among the patients, 58.4% were male and 41.6% were female; very similar percentages were found in the

TABLE I. Distribution of the Patients and the Controls According to Age and Sex

	Patients, no. (%)	Controls, no. (%)	Chi-square (*P*)
Age			
<65	32 (18.5)	38 (21.6)	
65–74	48 (27.8)	56 (31.8)	
75–84	75 (43.4)	73 (41.5)	
≥85	18 (10.4)	9 (5.1)	4.13 (0.24)
Total	173 (100)	176 (100)	
Sex			
Male	101 (58.4)	101 (57.4)	
Female	72 (41.6)	75 (42.6)	0.04 (0.85)
Total	173 (100)	176 (100)	

group of the controls, i.e., 57.4% and 42.6%, respectively. No seasonal predilection for herpes zoster was identified. Among the patients, 137 (79.1%) had a memory of primary infection with varicella zoster virus versus 139 (78.9%) of the controls. The involved dermatomic areas included the following: thoracic (90 cases [52.1%]), trigeminal (43 cases [24.9%]), cervical (20 cases [11.5%]), lumbar (16 cases [9.2%]), and sacral (4 cases [2.3%]) regions. The interviews revealed the occurrence of a recent physical trauma in 7.5% of the patients and 7.4% of the controls, and of a stressful event in 23.12% of the patients and 24.4% of the controls in 3 months preceding the onset of acute zoster or the interview, respectively. The patients with post-herpetic neuralgia who referred a low-, moderate- or high-grade disease were 39 (22.5%), 77 (44.5%), and 57 (33%), respectively.

The distribution of the patients and the controls according to a family history of herpes zoster is reported in Table II.

It can be seen that similar proportions of the patients and the controls reported a family history of herpes zoster irrespective of the degree of relationship, i.e., 17.4% and 18.2%, respectively, by analyzing only the first-degree relatives [RR 1.03 (CI 95%: 0.78–1.37)], and 28.4% and 29.6%, respectively, by analyzing the total number of relatives [RR 1.03 (CI 95%: 0.81–1.31)].

DISCUSSION

Reactivation of latent varicella zoster virus as herpes zoster is thought to result from waning of specific cell-mediated immunity, but little is known about its determinants in individuals with no underlying immunosuppression [Morenz et al., 1980; Nagasawa et al., 1990; Alliegro et al., 1996; Thomas and Hall, 2004]. A recent study investigated genetic susceptibility to zoster, analyzing polymorphisms at the promoter region of the gene for interleukin 10, a cytokine known to downregulate cell-mediated immunity [Haanpaa et al., 2002], and showed that a significantly higher proportion (53%) of 60 immunocompetent patients with herpes zoster carried the ATA haplotype at this region of the gene compared with 152 (38%) of 400 blood donors. A previous work had shown that HLA class I alleles may indeed control the immune response against varicella zoster virus and therefore the pathogenesis of post-herpetic neuralgia [Ozawa et al., 1999]. Another study on herpes simplex virus type 2 and neuralgia showed that patients with certain haplotypes and low levels of IgG3 and IgG1 have more frequent recurrences than controls and other patients with herpes simplex virus infection [Seppanen et al., 2006]. Finally, a genetic etiology for herpes simplex encephalitis in two children with autosomal recessive deficiency in the intracellular protein UNC-93B, resulting in impaired cellular interferon-α, -β, and -λ antiviral responses, has been recently proposed [Casrouge et al., 2006].

However, only a few data exist about family history and herpes zoster [Thomas and Hall, 2004]. Hicks et al. [2008] have published recently data on the distribution of patients with herpes zoster and controls according to family history of herpes zoster. In that study, 39.3% of the patients reported a family history of herpes zoster versus 10.5% of the controls, and a dose-dependent effect between having a single blood relative or multiple blood relatives with a history of herpes zoster was documented.

The results of the present study do not identify family history as a risk factor for herpes zoster, as a considerable proportion of the patients (28.4%) and a similar percentage of the controls (29.6%) reported a family history of herpes zoster.

It is noted that whereas the percentages of the patients who reported a family history of zoster were relatively similar in the two studies (i.e., 28.4% in the present study vs. 39.3% reported by Hicks et al. [2008]), a percentage of controls with a positive family history of zoster much

TABLE II. Distribution of the Patients and the Controls According to a Family History of Herpes Zoster

		Patients			Controls	
No. of first-degree relatives	No. of subjects	%	Chi-square (*P*)	No. of first degree-relatives	No. of subjects	%
0	143	82.7	0.04 (0.83)[a]	0	144	81.8
1	25	14.5		1	31	17.6
2	3	1.7			1	0.6
3	2	1.2				
Total	173	100		Total	176	100
		Patients			Controls	
All relatives	No. of subjects	%	Chi-square (*P*)	No. of first degree-relatives	No. of subjects	%
0	124	71.7	0.06 (0.80)[a]	0	124	70.5
1	38	22.0		1	38	21.6
2	6	3.5		2	10	5.7
3	4	2.3		3	3	1.7
4	1	0.6		4	1	0.6
Total	173	100		Total	176	100

[a]Versus all the other groups.

higher than that found by Hicks et al. [2008] was found in the present study (i.e., 29.6% vs. 10.5%, respectively).

It is difficult to speculate on the possible reasons for the discrepancy of the two studies, but some possible conclusions may be drawn.

It should be noted that the population sample examined by Hicks et al. [2008] was significantly younger (36.3% of the patients and 31.8% of the controls were over 65 years of age) than that examined in the present study, where more than 80% of the patients and the controls were over 65 years of age. It is known that the lifetime risk of developing herpes zoster is about 20–30%. However, the risk increases markedly with age, approximately doubling for each decade after 50 years of age [Donahue et al., 1995]. Several other studies also indicate an older age to be an independent predictor of post-herpetic neuralgia [Johnson and Dworkin, 2003]. In the present study the patients were affected by post-herpetic neuralgia, which usually follows severe acute herpes zoster, and this represents the second major difference between the present study and that of Hicks et al. [2008], who analyzed data from individuals generically defined as zoster patients. It can be expected that patients affected by post-herpetic neuralgia, i.e., a complicated form of herpes zoster, are more likely to remember possible cases of herpes zoster in their relatives. In the present study, 77.5% of the patients reported a moderate- or high-grade disease. It is also conceivable that older patients with herpes zoster have older relatives with a consequent higher probability of herpes zoster, when compared with the population studied by Hicks et al. [2008]. The third difference between the present study and that of Hicks et al. [2008] is represented by a different proportion of male and female subjects, even though it is difficult that it can account for the different results of the two studies. The association between sex and risk of herpes zoster has been widely investigated. In some studies women appear to have an increased incidence of zoster and post-herpetic neuralgia [Hope-Simpson, 1975; Meister et al., 1998; Chidiac et al., 2001; Jung et al., 2004; Chapman et al., 2003]. However, Dworkin and Shmader [2001] did not find sex differences associated with the various aspect of herpes zoster, with the only exception of the intensity of acute pain which is higher in the female gender than in males, as also confirmed in a recent study [Volpi et al., 2007]. In another study it was found that among patients with post-herpetic neuralgia there were more females than males, similarly to what happened in patients without post-herpetic neuralgia, but also more people over 60 years of age than in the group of patients without post-herpetic neuralgia [Volpi et al., 2008]. It seems conceivable that the earlier reported association between gender and long-term pain may have been a consequence of the fact that more women are in the higher age strata [Johnson and Dworkin, 2003]. In conclusion, the excess of male patients included in the present study, which can be related to the particular setting, is presumably not important for the evaluation of the final results.

The present study has some potential limitations. One of these is represented by the relatively low number of patients examined. However, it has to be considered that they were affected by post-herpetic neuralgia, which complicate a minor fraction of zoster cases. Next, it is worth mentioning the possibility of recall bias, which is inherent to any study in which subjects are asked to recall events that may have occurred many years before [Hicks et al., 2008]. However, in the present study, both the patients and the controls were given identical questionnaires and memory aids to determine whether their relatives had a history of herpes zoster. Interestingly, the percentage of the controls who referred a family history of herpes zoster was three times that reported in the study of Hicks et al. [2008], thus suggesting a low probability of recall bias in the population sample studied. Notwithstanding all these limitations, the results of the present study, which has been performed in patients affected by post-herpetic neuralgia, indicate that the most severe clinic forms of herpes zoster are not associated with a positive family history of herpes zoster.

Further and larger prospective cohort studies are needed to ascertain whether a family history of herpes zoster is really an independent predictor of zoster in different geographical settings. This may be very important, especially in relation to the availability of the zoster vaccine. The lack of conclusive data on familial risk factors for developing herpes zoster does not allow the selection of people who can benefit more from vaccination. It remains to be explored the attitude of the relatives of zoster patients regarding the zoster immunization.

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