Herpes Zoster and Multiple Sclerosis

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ABSTRACT: ***Background:*** Clinical experience suggests that young multiple sclerosis patients may have herpes zoster (HZ) earlier and more often than the general population. As there is evidence of a relationship between varicella zoster virus (VZV) and MS, a study of HZ and MS was undertaken. ***Methods:*** Eight hundred and twenty-nine patient-members of the Manitoba Chapter of the Canadian Multiple Sclerosis Society were surveyed by mail. Six hundred and thirty-three (76%) responded. Questions included: age at diagnosis of MS, history of HZ (yes, no, probably), number of episodes of HZ and age at each occurrence, date of birth, and sex of respondent. The controls were consecutive patients with other neurological diseases (OND) attending local neurological or neurosurgical clinics, plus practice-based and population-based surveys of herpes zoster without reference to any other disease. The OND controls were assessed at the time of their outpatient visits. ***Results:*** In the MS group with a positive/probable history of HZ, the HZ/MS rate was 106/633 (16.8%); in the practice-based survey the rate was 192/3534 (5.4%); and among the patients with OND it was 42/616 (6.8%). The HZ occurred at an earlier age in the MS group. The majority of male patients had HZ prior to the diagnosis of MS. The date of diagnosis is more likely to be a precise memory as opposed to the onset of symptoms. More than one attack of HZ was also more common in the MS group. ***Conclusions:*** This survey adds to the evidence that patients with MS have a unique relationship with the herpes zoster virus.

RÉSUMÉ: Herpes Zoster et sclérose en plaques. ***Introduction:*** L'expérience clinique suggère que les jeunes patients atteints de sclérose en plaques (SEP) sont susceptibles de souffrir du zona plus tôt et plus souvent que la population en général. Comme il semble exister une relation entre l'herpesvirus varicellae (HVV) et la SEP, nous avons effectué une étude sur le zona et la SEP. ***Méthodes:*** Notre enquête postale a porté sur huit cent vingt-neuf patients, membres du chapitre manitobain de la Société canadienne de la sclérose en plaques. Six cent trente-trois patients (76%) ont répondu. Les questions suivantes figuraient au questionnaire: l'âge au moment du diagnostic de SEP, l'histoire de zona (oui, non, probablement), le nombre d'épisodes de zona et l'âge au moment de chaque épisode, la date de naissance et le sexe des répondants. Des patients atteints d'autres maladies neurologiques (AMN), qui se sont présentés de façon consécutive à une clinique neurologique ou neurochirurgicale locale, des études en milieu extra-hospitalier et des études de population sur le zona sans référence à toute autre maladie, ont servi de contrôles. Les contrôles AMN ont été évalués au moment de leur visite à la clinique externe. ***Résultats:*** Dans le groupe SEP ayant une histoire positive/probable de zona, le taux de zona/SEP était de 106/633 (16.8%); dans l'étude extra-hospitalière le taux était de 192/3534 (5.4%); et parmi les patients AMN il était de 42/616 (6.8%). Le zona se retrouve à un âge plus précoce dans le groupe SEP. La majorité des hommes avaient eu leur zona avant le diagnostic de SEP. La date du diagnostic était plus susceptible d'être un souvenir précis contrairement au début des symptômes. Il était plus fréquent d'observer plus d'un épisode de zona dans le groupe SEP. ***Conclusions:*** Cette étude appuie l'observations que les patients qui ont une SEP ont une relation particulière avec le virus de l'Herpes Zoster.

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In a treatment trial of 50 patients with multiple sclerosis (MS), 10 reported a history of herpes zoster (HZ).[1] Eight had HZ before the onset of MS and one had two attacks. There are suggestions in the literature of a MS-varicella zoster virus (VZV) relationship.[2-4] There is a significant geographic correlation between the prevalence of MS and varicella in North America. Both have diminishing occurrence from north to south.[5] A distinctive population group in Western Canada has significantly less varicella, MS and HZ than their neighbours.[6] In the tropics, varicella is often a disease of late onset (average age 26), low contagion, and is relatively uncommon. In these countries MS is extremely rare.[7]

METHODS

A confidential, four-line questionnaire was mailed to the 829 patient-members of the Manitoba Chapter of the Multiple Sclerosis Society of Canada. The questions were: age and sex of the respondent; age at diagnosis of MS; a history of shingles (answers: yes, probably, no); if yes, at what ages did the shingles occur and how many times? There was no other identifying information requested. Any responses with the same date of birth, sex, and dates of MS and HZ were presumed to be duplicates and only one was kept. There were 633 responses (76%), 463 female. The controls were unselected patients with other

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neurological diseases (OND) attending local neurological and neurosurgical outpatient clinics. When they had completed their outpatient appointments they were asked if they would take part in a four-question survey. The only information offered was: complete confidentiality, the survey was not related to their present illness, and was entirely voluntary. Ninety-eight percent agreed to participate and were then handed a questionnaire asking – age and sex; have you had shingles (answers: yes, probably, no); if yes, at what age and how many times? No assistance was offered by the surveyor. Six hundred and sixteen OND patients were surveyed (Table 1). Three hundred and twenty-two were female (52%), a lower percentage than MS patients (63%). These patients were also found to be generally older.

The MS patients were also compared to a reported practice-based study and a population-based study with respect to age at diagnosis and number of episodes of HZ.[8,9] The mail and OND surveys were approved by the Ethics Committee of the University of Manitoba, Faculty of Medicine, and the Board of Directors of the Manitoba Chapter of the Multiple Sclerosis Society of Canada gave permission for the mail survey. No participating patient was identified. Consent was obtained from all patients and controls according to the Declaration of Helsinki.

Statistical Methods

HZ rates between groups were compared by calculating odds ratios and 95% confidence intervals, along with a chi-square test. Mantel-Haenszel stratified analysis by age and sex was performed along with homogeneity of odds ratios assessed by the Breslow-Day test.[10] Logistic regression analysis also provided age and sex adjusted ratios. Age specific rates from published population[8,9] were used to generate expected rates of HZ in the MS samples and OND controls. These expected numbers in the MS sample were then compared to the actual positive HZ cases by chi-square test. Significance levels were set at alpha = 0.05. Analyses were computed using SAS 6.12 (SAS Institute, Cary N.C.) and Statxact (Cytel Software Corporation).

Table 1: Sex and age distribution of the two studied groups – patients with MS and Other Neurological Diseases.

Survey Demographics

	MS		OND	
Age	**Males**	**Females**	**Males**	**Females**
<14	0	0	1	1
15-24	1	4	11	21
25-34	12	43	32	45
35-44	27	147	39	70
45-54	74	137	62	48
55-64	32	79	45	52
65-74	20	41	53	48
>75	5	12	51	37
TOTAL	**171**	**462**	**294**	**322**
mean +/- sd	51.3+/-11.5	48.1+/-12.1	55.2+/-17.6	50.6+/-17.9

Results

The two surveyed groups were not precisely comparable. Of the 616 OND patients, 322 were female (52%), a lower percentage than MS patients (63%). The OND patients were generally older. As HZ increases with age, this alone makes the increased HZ in the young MS group even more significant. The most common features of the two groups were: they live in the same community, and both attend neurological or neurosurgical physicians.

Herpes zoster among the MS patients was defined in two ways: those with a positive history of herpes zoster (72/633); and those with a positive and/or probable history of herpes zoster (106/633). An objective was to determine the age of onset of HZ among the MS groups and therefore only MS patients with a positive HZ history were assessed for this. The survey included the question of whether the HZ preceded or followed the diagnosis of MS because many MS patients receive corticosteroids or other immune system modifying medications.

The rate of HZ in the MS group with a positive and/or probable history of HZ was 106/633 (16.8%). In a practice-based survey, without reference to any other disease, the reported rate was 192/3534 (5.4%),[8] and in a group of patients with other neurological diseases it was 42/616 (6.8%) (Table 2). The HZ rates in the MS group compared to the OND group stratified by age groups and sex are homogeneous, giving an odds ratio of 2.61:1. In the study of Hope-Simpson[8] case ascertainment was by personal contact in a 3500 member rural and urban practice panel over 15 years.

The incidence of HZ (positive only) among MS patients was 232.5 per 100,000 patient-years, giving an odds ratio of 1.86:1 relative to the population-based study of Ragozzino et al.[9] in Rochester, Minnesota.

The age of onset of HZ in the MS group with a positive history of HZ is markedly different from the report of Ragozzino et al.[9] shown in Table 3A. The data consist of number of male and female cases of expected HZ by decades based on a population-based survey compared to the observed number from the current

Table 2: Comparison of the rates of herpes zoster (HZ) in a group of patients with multiple sclerosis (MS), a practice-based survey without reference to any other disease, and a group of patients with other neurological diseases.

Comparison of Rates of Herpes Zoster in Four Groups

Multiple Sclerosis Patients	**Practice-based Survey [8]**	**Other Neurological Diseases**
Positive history HZ N72/633 = 11.4%	N192/3534 = 5.4% *(Compared to MS patients positive HZ history only)	N42/616 = 6.8% **(Compared to MS patients positive HZ history only)
Positive & Probable History of HZ N106/633 = 16.8%		

* p < 0.0001 Odds Ratio (95% Confidence Interval = 2.23 (1.68, 2.97)
p = 0.005 Odds Ratio (95% Confidence Interval = 1.75 (1.18, 2.61)
** p = 0.0001 Odds Ratio Adjusted for Age and Sex (95% Confidence Interval) = 2.610 (1.79, 3.80)

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Table 3A: Number of multiple sclerosis patients with herpes zoster and age of onset of herpes zoster in this study (observed) compared to the number from a population-based study[9] (expected). Numbers in parentheses are patients with herpes zoster prior to the diagnosis of multiple sclerosis. *The total observed number, 68, is less than the actual number, 72, as four patients omitted their ages at the time of the herpes zoster.

Multiple Sclerosis Patients Observed to have Herpes Zoster Versus the Expected Number

	Males			Females		
Age	**Expected[1]**	**Observed**	**Chi-Sq**	**Expected[1]**	**Observed**	**Chi-Sq**
<14	1.45	4(4)[2]	4.48	2.98	3(3)[2]	0.00
15-24	1.06	3(3)	3.55	3.92	7(6)	2.42
25-34	1.75	4(3)	2.89	3.85	12(3)	17.25
35-44	1.73	2(1)	0.04	2.34	11(4)	32.05
45-54	1.60	5(1)	7.22	4.15	4(1)	0.00
55-64	1.00	2(0)	1.00	2.08	4(0)	1.77
65-74	0.41	2(0)	6.17	1.07	4(0)	8.02
>75	0.04	0(0)	0.04	0.10	1(0)	8.10
TOTAL	**9.04**	**22(12)**	**25.39[3]**	**20.49**	**46(17)**	**69.61[4]**

[1]Expected values based on Ragozzino et al.[9]

[2]Numbers in brackets are observed herpes zoster prior to MS diagnosis.

[3]Male total series p = 0.00065 (x^2, 7 degrees of freedom).

[4]Female total series p = < 0.000001 (x^2, 7 degrees of freedom).

survey. Both male and female rates of HZ are significantly different throughout all decades. For males less than age 35 chi-sq = 10.92 for 2 degrees of freedom, p = 0.0042. For females chi-sq = 19.67, p = 0.00005.

For males, 90% (10/11) of the episodes of HZ occurred before age 35 and prior to the diagnosis of MS, while for females 55% (12/22) occurred prior to MS (Table 3B). In a comparison of the mean age of individual patients at onset of HZ in the MS group versus the patients with other neurological diseases, the findings were: males MS 35.6 years vs. OND 47.4 years, p = 0.042; and females MS 38.5 years vs. OND 51.9, p = 0.0051.

In Table 3B the age specific HZ rates are listed for the 633 MS patients included in the current study. Compared to the expected linear increasing trends described in a practice-based[8] and a population-based survey,[9] rates for males less than 35 and for females less than 44 years of age exceed expectations. From 45 the trend is as expected for both sexes. Age specific HZ rates for the OND controls, on the other hand, reflect a linear increasing trend.

The number of MS patients with two or more positive episodes of HZ was 11/72 or 15.3% vs. 9/192 or 4.7% in a practice-based survey.[8] Odds ratio 2.42 (0.99, 5.92) p = 0.053. In a population-based survey[9] the rate for patients with two or more episodes of HZ was 33/590 (5.5%), odds ratio for MS patients 2.73 (1.32, 5.64) p = 0.0070.

Concerning the MS patients with HZ and those without, there was no significant difference between these two groups in the age at diagnosis of MS, age at time of survey, or sex proportions.

Table 3B: The proportion of multiple sclerosis patients in this study (N 633) related to their sex and age of onset of herpes zoster compared to control patients (N 616).

Age of Onset of Herpes Zoster in a Group of Patients with Multiple Sclerosis and Other Neurological Diseases

	MS		OND	
Age	**Males**	**Females**	**Males**	**Females**
<14	2.3%	0.9%	0.3%	0.0%
15-24	1.8	1.5	0.3	0.6
25-34	2.4	2.8	0.7	1.0
35-44	1.9	3.2	1.6	1.2
45-54	3.0	1.9	1.9	1.6
55-64	1.8	3.8	4.0	2.9
65-74	8.0	7.5	1.9	4.7
>75	0.0	8.3	0.0	8.1

Discussion

There is general consensus that a childhood environmental factor exists in multiple sclerosis. The purpose of the current study was to enquire if there was any relationship between one of the manifestations of varicella zoster virus infection, namely herpes zoster, and MS.

This study showed that a significant number of patients with MS have a different history of HZ than the non-MS population. Herpes zoster is more common in MS, occurs at an earlier age, and has more repeated attacks than in the non-MS population.

The other relationships between MS and the varicella zoster virus, i.e., ages of onset, geography and climate, have been described elsewhere.[2-3,5-7]

The distribution of HLA antigen frequencies in the geographic area of this study has not been published. However, the data compiled by the local Organ Transplant, Immunology Laboratory reveal frequencies of antigens A2 (22%), B7 (16%), and DQ1 (60%). This information is derived from tissue typing of over 200 donors and 200 recipients and are averages for the two groups.[11] A distinctive and isolated racial group, the Hutterite Brethren, have highly significantly less varicella, herpes zoster, and MS than their neighbours.[6] Nevertheless, they have gene frequencies of greater than 10% for antigens A3, DR2, and DQ1.[12] The paucity of varicella and herpes zoster, and the accompanying low varicella antibodies,[13] are due to the Hutterite practice of confining their children exclusively to the Colonies for educational purposes up to age 14. After this age the rate of varicella in the larger community is very small.[14] Whether raising children in this restricted environment has anything to do with their significantly lower rate of MS as adults is unknown.

Conclusions

This paper adds evidence to a possible relationship between herpes zoster virus infection and multiple sclerosis. It is part of a number of studies that support this possible relationship. These are:

1) In North America where varicella is common so is multiple sclerosis and where varicella is less common so is multiple sclerosis.[5] There are no reports or areas where MS is common and varicella is rare. 2) There is a north to south diminishing gradient of both diseases in North America. For example, at latitude 52 degrees N, MS is 11 times more common than at latitude

30 degrees N. The frequency of varicella at these two latitudes parallels the MS rates. 3) In some tropical countries where multiple sclerosis is almost unknown, varicella is an adult disease of low contagion, unlike northern North American varicella.[7] 4) A racially exclusive group (the Hutterite Brethren) that by geographic location and genetic make-up should have a high incidence of multiple sclerosis have a statistically significant lesser amount of the disease and less varicella and herpes zoster.[6] 5) A possible explanation for the above is the fact that Hutterite children are kept on the Colonies for educational purposes and are relatively free of varicella until age 14. At this age varicella in Canada is finished as an epidemic disease.[14] 6) In addition to the population-based epidemiological information in 4 (above), a varicella zoster virus antibody study of Hutterites and controls revealed that many Hutterites are VZV seronegative.[13] 7) Finally, the present paper adds one more apparent connection between MS and a VZV manifestation. Perhaps the potential or actual MS patient has less ability to contain the varicella zoster virus than the rest of the population. May the VZV act as an antigen mimic in these patients, as well as provoking herpes zoster in some of them at an unusually early age? Whatever the mechanism or relationship between the VZV and MS is it true that no one will develop MS if they have not had a prior VZV infection?

Appendix

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