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Seasonal variation of multiple sclerosis exacerbations in Japan.

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Several reports have described the seasonal variation of multiple sclerosis (MS) attacks in the European countries and in the US. Some have insisted that attacks occurred more frequently in winter or spring. We investigated the possibility of a seasonal variation in the frequency of MS attacks among patients in Japan. A total of 172 MS exacerbations in 34 MS patients were analyzed retrospectively. Attacks were divided into two groups: opticospinal type and brain type. The 12 months of the year were assigned to 6 groups based on average monthly temperature. Of the 172 MS exacerbations, 123 were opticospinal type and 49 were brain type of attacks. The total number of attacks was significantly more frequent in the warmest (July and August) and coldest (January and February) months. The heat of summer in warmer, low latitude areas may be a risk factor for MS attacks.

PMID: 14767690 [PubMed - indexed for MEDLINE]

Neurology. 1983 Jun;33(6):697-701. Links

Seasonal variation of multiple sclerosis exacerbations in Arizona.

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We studied 178 MS patients and 82 controls for 5 years. A monthly pattern in in the frequency of exacerbations in Arizona differed from the patterns seen in other regions of the world. Exacerbations were most common in warmer months. No explanation for this was found. In this prospective study, the frequency of viral infections in the MS patients was lower than in the controls.

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[Seasonal variations in the outbreaks in patients with multiple sclerosis]

[Article in Spanish]

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INTRODUCTION: It has been suggested that there is an environmental factor at play in the aetiology and pathogenesis of multiple sclerosis (MS) that acts as an essential component of the disease process, and a number of studies also point to a relationship between the seasons of the year and the appearance of outbreaks. AIMS: Our aim was to study the possible relation between seasonal variations and the appearance of outbreaks in patients with relapsing-remitting forms of MS. PATIENTS AND METHODS: We studied 31 patients over the period between 1997 and 2002 and calculated the monthly and quarterly rate of incidence of outbreaks. The statistical evaluation of the results was performed by applying the Chi-squared test. RESULTS: We observed a higher incidence of outbreaks in the summer months (more in June) and a lower incidence in winter (less in December), with statistically significant differences. CONCLUSIONS: In our patients, outbreaks of MS are related to seasonal variations, with a higher number in the warmer months and fewer in the colder months.

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BRIEF COMMUNICATION

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Seasonal variation of multiple sclerosis exacerbations in Japan

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Abstract Several reports have described the seasonal variation of multiple sclerosis (MS) attacks in the European countries and in the US. Some have insisted that attacks occurred more frequently in winter or spring. We investigated the possibility of a seasonal variation in the frequency of MS attacks among patients in Japan. A total of 172 MS exacerbations in 34 MS patients were analyzed retrospectively. Attacks were divided into two groups: opticospinal type and brain type. The 12 months of the year were assigned to 6 groups based on average monthly temperature. Of the 172 MS exacerbations, 123 were opticospinal type and 49 were brain type of attacks. The total number of attacks was significantly more frequent in the warmest (July and August) and coldest (January and February) months. The heat of summer in warmer, low latitude areas may be a risk factor for MS attacks.

Key words Multiple sclerosis • Seasonal variation • Risk factor

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Introduction

Several studies regarding the seasonal variations of multiple sclerosis (MS) exacerbations have been reported, mainly from Europe and the United States. Some reported that MS attacks occurred at an uneven frequency across the seasons with higher incidence in winter or spring [1–3], whereas others reported that there were no significant seasonal variations [4-6]. Most reports have suggested that seasonal environmental factors and probable infectious factors, as yet undefined, are related to attacks, while some reports have shown that viral infections are associated with the timing of MS attacks [1, 2]. Many of these studies were performed in high latitude regions more than 40° N where the prevalence of MS is high [1–3]. We found only a few reports from regions less than 40° N, for example from Arizona [7, 8]. We also found a study of seasonal variations of MS in Japan reported more than 30 years ago [5]. We further investigated the seasonal variation in MS attacks in a group of patients living at a latitude of 35° N.

Materials and methods

We retrospectively studied 34 patients with MS living in Tokyo and Saitama (latitude, 35° N). Patients were inpatients or outpatients attending the National Defense Medical College Hospital for medical examinations and therapies. MS was diagnosed according to the guidelines of the International Panel on the Diagnosis of Multiple Sclerosis [9].

Exacerbation was defined as the appearance of a new symptom or worsening of an old symptom attributable to MS lasting ≥24 hours, without fever, accompanied by a new neurogenic abnormality, and preceded by stability or improvement for ≥30 days [10]. We carefully excluded those attacks in which we suspected that the temporary increase of symptoms was due to hot temperature based on clinical course and results on magnetic resonance imaging (MRI).

We divided the patients' attacks into two groups based on their clinical features and major sites of demyelination on MRI (high intensity areas on T2-weighted images) that could explain the symptoms of the patients. Therefore, attacks of "brain type" involved demyelinated lesions in the brain, while "opticospinal type" of attacks involved lesions of the optic nerve or spinal cord. If both brain and opticospinal attacks occurred simultaneously, we classified them according to the clinical symptoms.

To analyze the relationship between average monthly temperature and frequency of MS attacks, we assigned the 12 months of the year to 6 groups based on average monthly temperature: <7.5°C, January and February; 7.6°–10.0°C, March and December; 10.1°–15.0°C, April and November; 15.1°–20.0°C, May and October; 20.1°–25.0° C, June and September; and >25.1°C, July and August.

Statistical analysis was performed using the chi-square test.

Results

We retrospectively studied seasonal variations in MS exacerbations in 12 men and 22 women of average age 42.6 and 40.8 years, respectively. Mean duration of illness was 7.6 and 7.9 years, respectively. Between 1986 and 2002, the patients experienced 172 attacks, of which 123 were opticospinal type and 49 were brain type (Fig. 1). The incidence of attacks was highest in July, but the monthly pattern was not statistically significant (total attacks, χ^2=18.57, p>0.05; opticospinal attacks, χ^2=13.50, p>0.05; brain attacks, χ^2=9.70, p>0.05).

In order to investigate the relationship between environmental temperature and attacks, we grouped the 12 months of the year into 6 subgroups according to average monthly temperature (Table 1). When considering all 172 MS exacerbations, the attacks were significantly more frequent in the warmest (July and August) and coldest (January and February) months (χ^2=11.70, p<0.05); when the attacks were distinguished according to type, there was a non-significant tendency for more attacks to occur in the warmest and coldest months (brain lesions, χ^2=4.51, p>0.05; opticospinal lesions, χ^2=7.59, p>0.05).

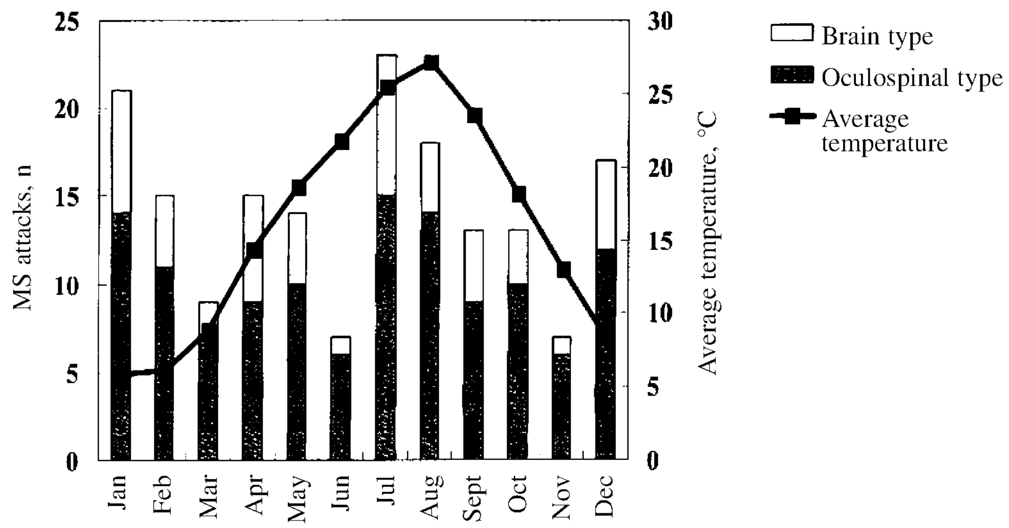

Fig. 1 Distribution of 172 MS attacks in 34 patients, by month. The line shows the average monthly temperature in Tokyo. The attacks are most frequent in July, but not significantly so

Table 1 Distribution of 172 MS attacks in 34 patients, by average monthly temperature

Average temperature, °C	Months	MS attacks, n		
		Brain type	Opticospinal type	Total*
>25.1	July and August	12	29	41
20.1–25.0	June and September	5	15	20
15.1–20.0	May and October	7	20	27
10.1–15.0	April and November	7	15	22
7.6–10.0	March and December	7	19	26
<7.5	January and February	11	25	36

* p<0.05, chi-square test

Discussion

The seasonal variations of MS exacerbations in patients living in Tokyo and Saitama in areas (below 40° N) were different from the patterns observed by Satoyoshi et al. [5] among Japanese subjects in 1970. These authors reported that the onset of MS was higher between December and March with no apparent monthly pattern in exacerbations. In our study, MS patients experienced attacks significantly more frequently in the warmest and coldest months of the year.

The seasonal variations of MS attacks tend to be interpreted in terms of the probable infectious agents that can affect the host's immune system. However, Hopkins and Swank [4] stated that MS attacks were related to diurnal temperature range, suggesting that the attack frequency increased when the diurnal temperature range was large. On the other hand, Bamford et al. [8] observed that the exacerbations were more frequent in warm months in Arizona, and Jin et al. [3] found positive relationships between the number of attacks and both the temperature and the number of hours of sunlight per month. We also observed that attacks were more frequent in the warmest (and coldest) months. In the low latitude, warmer areas of Asia, warm temperature can also be a potent risk factor for the attacks. This hypothesis is supported by a report describing clinical improvement and a decrease in leukocyte nitric oxide production induced by the cooling-garment treatment in MS [11]. In regard to the high incidence of MS attacks in the coldest months, we assume that common infections occurring during the cold season, such as sinusitis, may play a role, as has been argued in previous reports [1, 2]. In Japan, flu-like episodes are most commonly seen in January and February.

It is difficult to compare our findings with those of the previously mentioned studies, because these reports used different criteria to diagnose MS and to define MS exacerbations and because there are also many differences in environmental factors, such as average monthly temperature, hours of sunlight and the prevalence of MS in each region. As the prevalence of MS in Japan is low, we could only study a small number of cases, in contrast to the reports from high-latitude regions where more MS patients exist. However, in Japan, opticospinal type of MS exacerbations, including Devic's disease, are more frequent than brain type of attacks [5], as reflected by the patients' attacks in the present study. Therefore, the study of patients gathered from the other low latitude areas might be useful to clarify the effect of environmental factors.

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NEUROLOGY

Seasonal variation of multiple sclerosis exacerbations in Arizona

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Article abstract—We studied 178 MS patients and 82 controls for 5 years. A monthly pattern in the frequency of exacerbations in Arizona differed from the patterns seen in other regions of the world. Exacerbations were most common in warmer months. No explanation for this was found. In this prospective study, the frequency of viral infections in the MS patients was lower than in the controls.

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Seasonal variation of multiple sclerosis exacerbations in Arizona

Colin R. Bamford, MD; William A. Sibley, MD; and Cole Thies, MSPH

In a retrospective study of the relationship between retrobulbar neuritis (RBN) and MS, Taub and Rucker[1] noticed that RBN tended not to develop in the winter months. Those who developed MS in the next 10 to 15 years also showed this seasonal variation.

Hopkins and Swank[2] in Montreal and Schapira[3] in Newcastle-upon-Tyne were unimpressed by the slight monthly fluctuation in incidence of exacerbations, but Prineas[4] later detected significant seasonal variation in Newcastle. Sibley and Foley[5,6] in Cleveland and Wuthrich and Rieder[7] in Switzerland confirmed the seasonal variation of MS attacks. Wuthrich and Rieder[7] attributed the different patterns to the location of the study.

The purpose of the present study was to determine whether location and season influence the occurrence of MS exacerbations.

Methods. Of a total of 178 MS patients seen in the MS clinic between January 1976 and December 1980, 82 had been registered constantly. These patients had probable or clinically definite MS,[8] were mentally intact, and were reliable informants. Eighty-two voluntary, nonfamilial, normal controls were age- and sex-matched to the constantly registered patients. Patients and controls were unaware of our interest in the seasonal variation of MS exacerbations. Every month a nurse questioned the patients about new symptoms and the severity of old symptoms. Patients and controls were asked about exposure to an altered environment and change in health, activities, or diet, using tested standardized questions presented verbatim by telephone, in person, or by mail. The nurse knew the identity of patients and controls.

Every 3 months and after every exacerbation, a neurologist examined the patients and completed a Kurtzke DSS form.[9] The incidence of exacerbations (new or accentuated symptoms lasting more than 24 hours) was calculated, corrected for the number of days in the month, and tabulated for each specific month of every year as well as the entire 5-year period.

The monthly variation in frequency of selected factors (expressed as number of episodes per month) was compared for the entire group of 178 MS patients and the 82 controls. The factors included remaining indoors, using air-conditioning (refrigeration), evaporative cooling (air cooled by passage through water-soaked pads), central heating, humidifiers, and dehumidifiers; sports, hiking, walking, unaccustomed exercise, and activity resulting in physical exhaustion; using a cane, crutches, or a wheelchair; contracting coryza, influenza, cold sores, shingles, gastroenteritis, urinary infections, and other infections; suffering major illnesses, allergies, anxiety, and depressive syndromes and confusion; and the use of tranquilizers, alcohol, tobacco, and drugs.

Finally, the group of 178 patients was randomly divided into two groups of 89 (groups 1 and 2) to explore the seasonal patterns of exacerbations by means of an artificial comparison. The purpose of the random allocation was to determine the monthly variation of frequency of exacerbation in groups 1 and 2 independently. Frequency of exacerbation was measured, using an index similar

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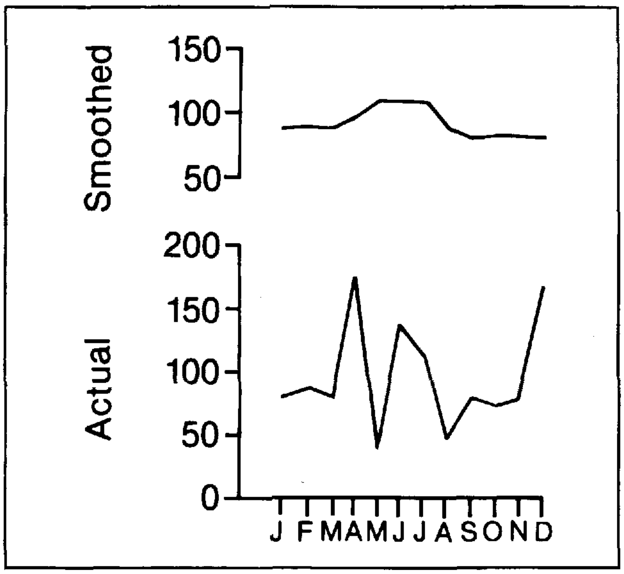

Figure 1. The monthly distribution of exacerbations in Arizona. Randomly selected first half of 178 MS patients (group 1).

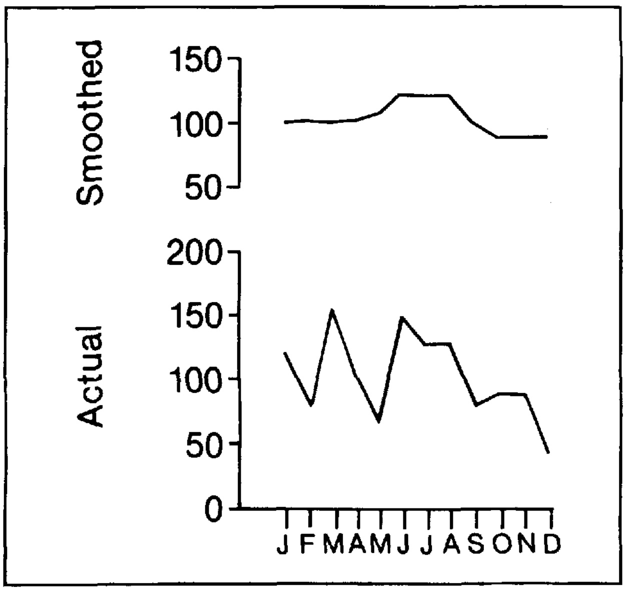

Figure 2. The monthly distribution of exacerbations in Arizona. Randomly selected second half of 178 MS patients (group 2).

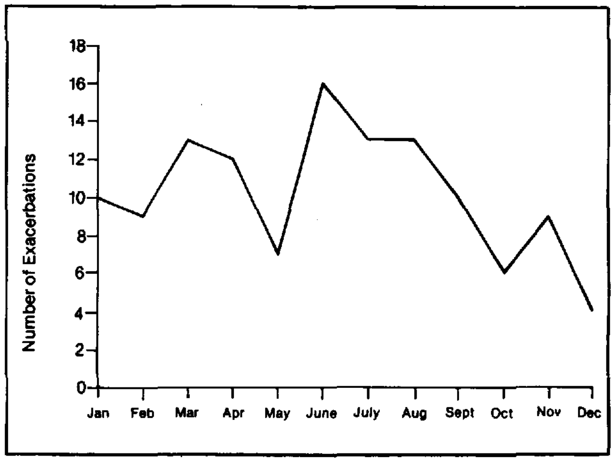

Figure 3. The monthly distribution of exacerbations in Arizona. Eighty-two patients observed constantly between January 1976 and December 1980 (group 3).

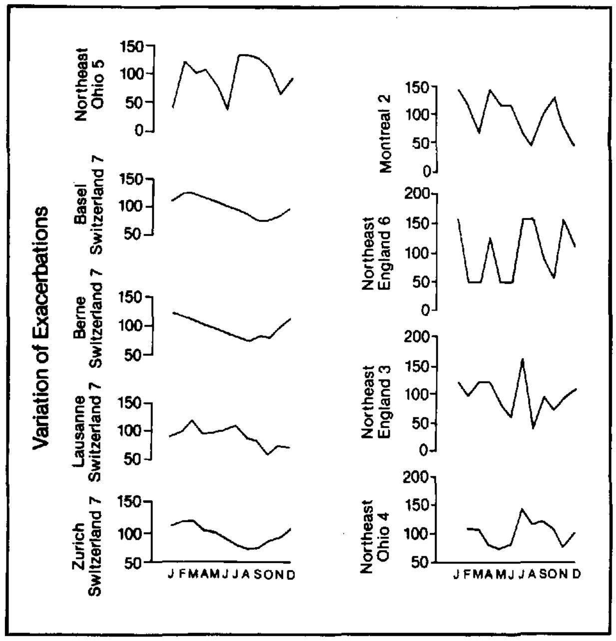

Figure 4. Monthly variation of MS exacerbations in varying regions. (The Swiss data has been smoothed.)

to that used by Wuthrich and Rieder.[7] (First, the number of exacerbations in each month was corrected for the number of patient months of observation. Then the corrected number of exacerbations was divided by the mean of all 12 months, and the resultant ratio was multiplied by 100 to produce the index. The index is used in figures 1, 2, 4, and 5.) If a similar pattern emerged in groups 1 and 2, this would be taken as evidence of some seasonal effect. The two monthly variations obtained were also compared to those reported from other geographic locations (Switzerland, Ohio, England, and Canada[2-7]).

The group of 82 constantly registered subjects was dealt with as an independent group (group 3) to ensure that the observations persisted with more prolonged follow-up. See table 1 for the demographic and clinical characteristics of the groups studied.

Results. *Prospective study of monthly variation of MS exacerbation episodes.* Patients in group 1 had peak exacerbation rates in April, June, July, and December and low rates in May and August (figure 1). Those in group 2 had peak rates in January, March, April, June, July, and August and low rates in May and December (figure 2). Thus, in general, inspection of these data reveals peak exacerbation rates in spring and summer in both groups. Patients in group 3 had peak rates in

March, April, June, July, and August and low rates in May and December (figure 3). There was a clustering of exacerbations such that a smaller proportion of patients contributed the majority of exacerbations, eg, 15% of the patients in group 1 accounted for 60% of the exacerbations, and 15% of the patients in group 2 accounted for 58% of the exacerbations; however, clustering did not contribute to the seasonal variation.

Using a smoothing technique[10] that consisted of a 3-month centered moving median, the exacerbation rate for any one month was calculated, and a smoothed curve was generated for groups 1 (figure 1) and 2 (figure 2). (Smoothing is the statistical manipulation of data which may be used to attempt to isolate a "signal" from overlying noise, although the technique may not always result in a true signal being generated.) Peaks were noted in May, June, and July for group 1 and in June, July, and August for group 2. Thus, the smooth curves also suggest a spring and summer predilection. A Pearson product-moment correlation coefficient, calculated for the smoothed curves of these two groups, was 0.77 (p = 0.022). No attempt was made to correlate group 3 with groups 1 and 2

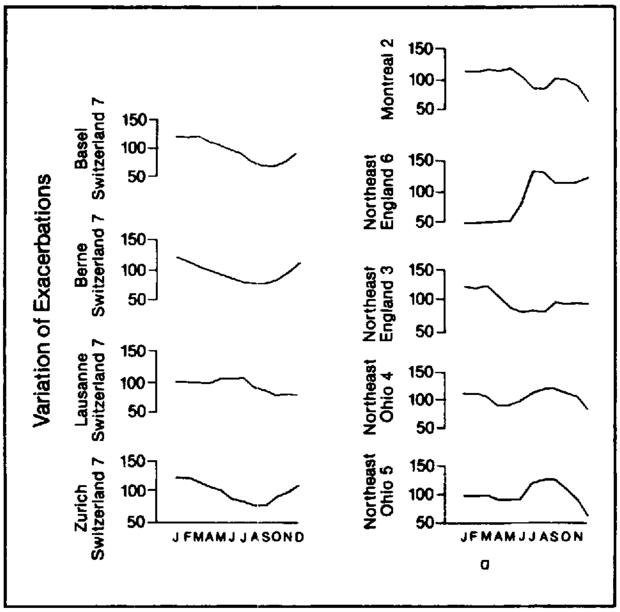

Figure 5. Monthly variation of MS exacerbations in varying regions subjected to a smoothing technique.

because they had subjects in common, and a high correlation would thus be anticipated.

Data from the literature (figure 4) were subjected to the same smoothing technique (figure 5),[2-7] and each pair of smoothed curves was examined for positive correlation, which was greatest and most frequent in groups studied within the same region. In addition to positive correlation observed between the two Arizona groups, the Ohio groups were significantly correlated (p = 0.001), and four of six potential comparisons obtained from four areas in Switzerland were significantly correlated (p = 0.001 to 0.006). The two studies performed in England did not show positive correlation. Thus 67% of within-region comparisons showed significant positive correlation, whereas only 20% of between-region comparisons did (figure 6).

Retrospective study of seasonal variation on onset of MS. Sibley and Paty[11] published brief results previously.

Prospective study of monthly variation of various epidemiological factors (table 2). More patients reported being involved in unaccustomed exercise from April to August (mostly swimming) and in November (comparison of patients and normal controls).

Unaccustomed exercise and exacerbations occurred within 2 months' association in 3.8% of patient-months. Exacerbations without unaccustomed exercise occurred in 2.8% of patient-months, which was not significantly lower (χ^2 = 2.3; p = 0.13). Unaccustomed exercise (usually swimming) is usually done in summer, so that the latter rate (2.8%) could be lower because it may be influenced by a higher proportion of winter months (comparison of specific patient-months, eg, patient Januaries).

We therefore analyzed the same data in a different way. The exacerbation rate for the periods at risk (2 months after unaccustomed exercise) was compared to the exacerbation rate at all other times for each individual patient. These comparisons included only the patients who were observed to be at risk and not at risk for periods exceeding 6 months each. The exacerbation rate for the patients when they were at risk was 0.47 exacerbations per year, and when not at risk it was 0.42, not statistically significant (p = 0.5 using a paired t test) (comparison of patients when at risk against

Table 1. Demographic and clinical characteristics of patient groups and controls

	Group 1		Group 2		Group 3		Controls	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age in years	49.8	12.5	50.7	11.7	50.2	13.3	49.5	13.4
Age at onset	31.6	10.6	31.4	9.1	31.4	10.4	N/A	N/A
Average Kurtzke DSS	5.4	2.6	5.1	2.5	5.5	2.6	N/A	N/A
Female:Male	1.6:1		1.9:1		1.6:1		1.6:1	

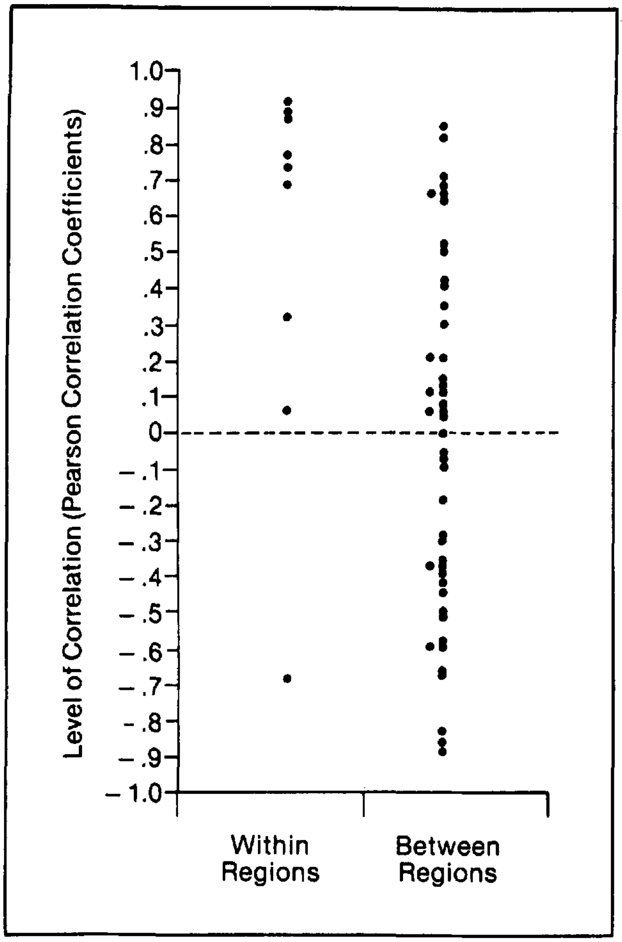

Figure 6. Correlation of exacerbation rates among the same and varying geographic areas.

themselves when not at risk).

Among other factors studied, there were some significant seasonal variations. The entire group tended to be free from "anxiety" in May and June and from "depression" or "frustration" from May to August (table 2; $p < 0.05$). The consumption of beer tended to be higher from June to September (table 2; $p < 0.05$); there was no monthly variation in the consumption of other alcoholic beverages (comparison of specific patient-months).

Naturally, refrigeration (effective cooling) and evaporative cooling (less effective) were commonly used during summer months. However, the monthly exacerbation rate for those using refrigeration was not significantly different from the rate for those using evaporative cooling (2% for refrigeration versus 3% for evaporative cooling ($\chi^2 = 0.719$; $p = 0.40$) (comparison of patients using refrigeration with patients using evaporative cooling).

Allergies occurred most commonly in April and May in both patients and controls (comparison of specific patient-months and specific control-months).

Common colds, influenza, cold sores, and diarrhea were reported more frequently by controls. Coryza was reported during 7% of patient-months and 13% of control-months ($\chi^2 = 87$; $p < 0.001$), influenza during 3% of patient-months and 5% of control-months ($\chi^2 = 36$; $p < 0.001$), cold sores during 2% of patient-months and 6% of control-months ($\chi^2 = 126$; $p < 0.001$), and diarrhea during 3% of patient-months and 6% of control-months ($\chi^2 = 67$; $p < 0.001$). Of the patients who did suffer

Table 2. Percentage of subject-months associated with specific factors

	Subject-specific factor	J	F	M	A	M	J	J	A	S	O	N	D
1	Pt remaining indoors	77	77	73	64	64	72	78	76	78	74	73	74
	C remaining indoors	73	75	73	71	66	66	67	67	67	66	71	74
2	Pt engaging in sports	8	9	9	13	13	21	23	23	16	11	11	10
	C engaging in sports	23	23	21	22	24	25	28	27	23	21	21	18
3	Pt engaging in unaccustomed exercise	11	8	11	13	13	17	13	15	11	11	13	11
	C engaging in unaccustomed exercise	11	10	11	13	9	13	6	10	8	7	11	8
4	Pt contracted colds	15	11	9	6	5	3	2	2	5	9	9	12
	C contracted colds	22	18	16	14	9	6	6	5	8	12	18	16
5	Pt contracted flu	7	5	5	2	2	2	1	1	1	3	2	5
	C contracted flu	10	8	6	6	5	4	3	2	3	4	4	10
6	Pt contracted cold sores	2	1	1	1	1	1	1	1	1	2	1	2
	C contracted cold sores	5	5	7	5	7	5	5	4	7	7	6	7
7	Pt contracted diarrhea	4	3	2	2	2	3	4	3	2	3	3	3
	C contracted diarrhea	6	7	4	6	5	5	6	8	4	6	6	7
8	Pt contracted UTI	7	4	5	3	4	4	6	4	5	6	5	4
	C contracted UTI	1	1	1	2	2	2	2	2	1	2	1	6
9	Pt suffering allergies	17	20	27	35	36	29	27	24	29	28	26	21
	C suffering allergies	20	22	24	28	28	30	27	24	36	32	31	24
10	Pt suffering anxiety	23	25	25	24	19	19	20	23	25	26	29	20
	C suffering anxiety	12	13	13	11	12	10	12	10	16	12	15	9
11	Pt suffering depression	19	20	19	17	12	15	13	15	20	19	19	15
	C suffering depression	14	13	17	12	13	12	13	14	16	13	15	10

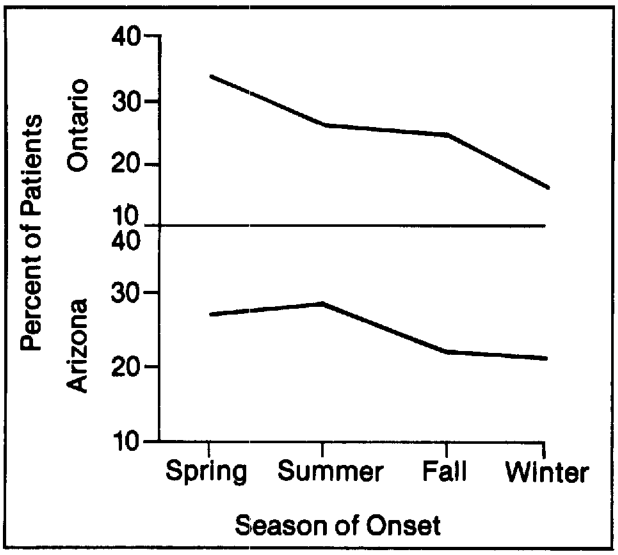

Figure 7. Surveys illustrating the percentage of patients having had the onset of MS during different seasons.

from them, coryza developed from October to March, influenza developed from December to March, and there was no monthly variation in occurrence of cold sores and diarrhea (comparison of specific patient-months with specific control-months).

Other factors studied did not occur with a significant or relevant monthly variation.

Discussion. The temporal variation in frequency of MS attacks may be influenced by the location of the population studied; smoothed patterns are usually rather similar for any two groups within the same area. Unfortunately, most interregional studies (including the present one) were performed by the same researchers.[5-7] However, different patient examiners were involved, eliminating part of the observer bias.

Sibley and Paty[11] published a retrospective study of the seasonal variation in onset of MS in Arizona and Canada in which they relied on patient recall. From our group of 178 patients, 130 reported the season of their disease onset. Twenty-seven percent of these patients claimed to have had the onset in spring, 28% in summer, 22% in fall, and 21% in winter. The seasonal variation in onset was not striking and did not achieve statistical significance. We did, however, contrast our results with those obtained from a group of patients in Ontario, Canada,[11] in which a statistically significant seasonal variation was identified, with onsets being most frequent in the spring and summer. The seasonal curves for the two regions (figure 7) are visually quite similar and, as expected, not significantly different from each other ($\chi^2 = 2.25$; $p = 0.52$). Failure to achieve statistical significance in our group as compared to the Ontario group could be explained by the longer mean duration of disease in our group[11] and more likely erroneous recall of remote events or by the ubiquitous type II error.

It was not possible to calculate a meaningful curve to illustrate the seasonal variation in onset of MS in patients residing in Arizona at the time of onset because of the small number of these individuals (28%).

We could not identify any epidemiological factors with a spring-summer occurrence closely corresponding to the temporal variation of exacerbations in Arizona other than summer heat, unaccustomed exercise, and the consumption of beer. All of these associations might be coincidental. Chronic overheating by patients in the summer months may cause more problems than the transient neurologic worsening attributed to heat.[12-14]

We noted a lower incidence of minor viral infections in MS patients than in controls, which could be due to either patient sheltering or strong immune defenses.

Although many of our patients reported that refrigeration of the home decreased the severity of long-standing symptoms, it did not appear to be more beneficial in influencing the exacerbation rate than the use of the evaporative cooling, generally a less efficient method of cooling.

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