NEUROLOGY

Seasonal variation of multiple sclerosis exacerbations in Arizona

Colin R. Bamford, William A. Sibley and Cole Thies

Neurology 1983;33;697-

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.

NEUROLOGY (Cleveland) 1983;33:697-701

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

From the Department of Neurology, University of Arizona College of Medicine, Tucson, AZ.

Accepted for publication October 7, 1982.

Address correspondence and reprint requests to Dr. Bamford, Department of Neurology, University of Arizona College of Medicine, Tucson, AZ 85724.

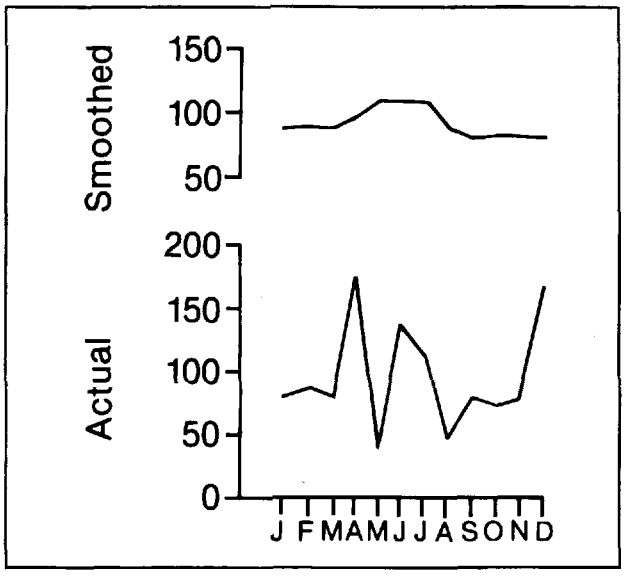

Figure 1. The monthly distribution of exacerbations in Arizona. Randomly selected first half of 178 MS patients (group 1).

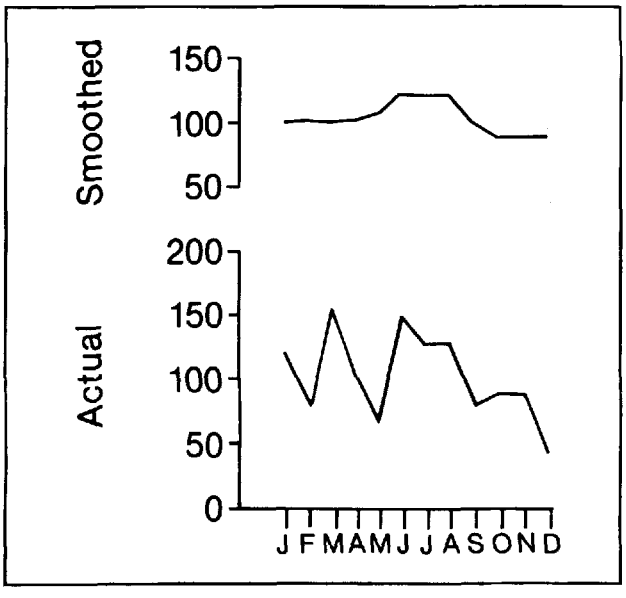

Figure 2. The monthly distribution of exacerbations in Arizona. Randomly selected second half of 178 MS patients (group 2).

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]).

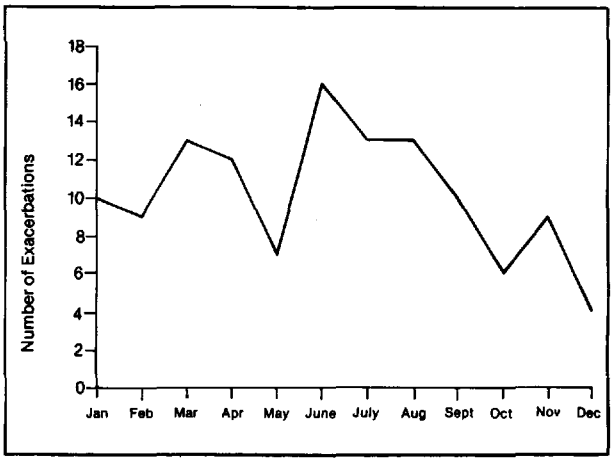

Figure 3. The monthly distribution of exacerbations in Arizona. Eighty-two patients observed constantly between January 1976 and December 1980 (group 3).

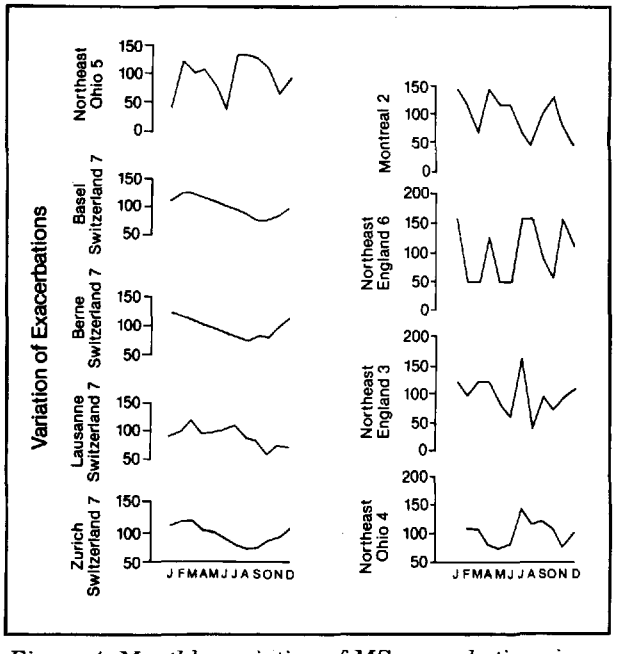

Figure 4. Monthly variation of MS exacerbations in varying regions. (The Swiss data has been smoothed.)

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

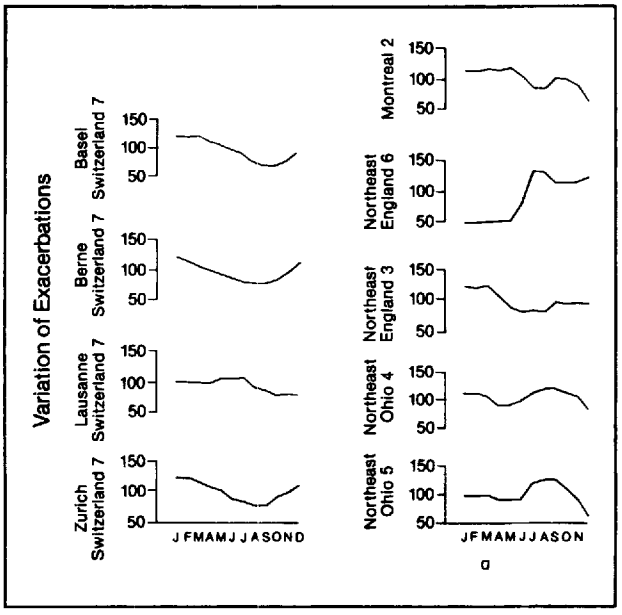

Figure 5. Monthly variation of MS exacerbations in varying regions subjected to a smoothing technique.

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 ($\chi^2 = 2.3$; $p = 0.13$). 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	

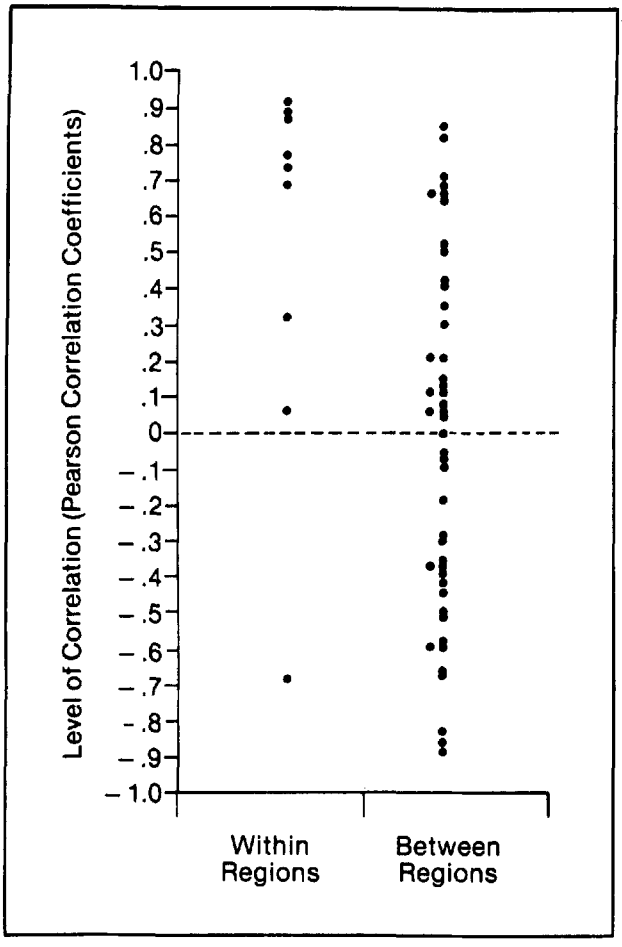

Figure 6. Correlation of exacerbation rates among the same and varying geographic areas.

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

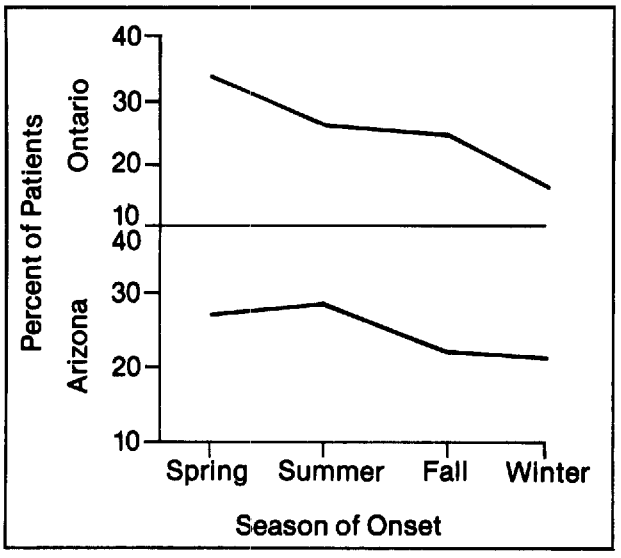

Figure 7. Surveys illustrating the percentage of patients having had the onset of MS during different seasons.

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.

References

1. Taub RG, Rucker CW. The relationship of retrobulbar neuritis to multiple sclerosis. Am J Ophthalmol 1954;37:494-7.
2. Hopkins CE, Swank RL. Multiple sclerosis and the local weather. AMA Arch Neurol Psychiatr 1955;74:203-7.
3. Schapira K. The seasonal incidence of onset and exacerbations in multiple sclerosis. J Neurol Neurosurg Psychiatry 1959;22:285-6.
4. Prineas JW. The etiology of multiple sclerosis. In: Vinken JP, Bruyn GW, eds. MS and other demyelinating diseases. Amsterdam: North Holland, 1970:118-20.
5. Sibley WA, Foley JM. Infection and immunization in multiple sclerosis. Ann NY Acad Sci 1965;122:457-68.
6. Sibley WA, Foley JM. Seasonal variation in multiple sclerosis and retrobulbar neuritis in northeastern Ohio. Trans Am Neurol Assoc 1965;90:295-7.
7. Wuthrich R, Rieder HP. The seasonal incidence of multiple sclerosis in Switzerland. Eur Neurol 1970;3:257-64.
8. Rose AS, Ellison GW, Myers LW, Tourtellotte WW. Criteria for the clinical diagnosis of multiple sclerosis. Neurology (Minneap) 1976;26:20-2.
9. Kurtzke J. Further notes on disability evaluation in multiple sclerosis, with scale modifications. Neurology (Minneap) 1965;15:654-61.
10. Tukey JW. Exploratory data analysis. Reading, MA: Addison-Wesley, 1977:205-36.
11. Sibley WA, Paty DW. A comparison of multiple sclerosis in Arizona (USA) and Ontario (Canada)—preliminary report. Acta Neurol Scand [suppl 87] 1981;64:60-5.
12. Simons DJ. A note on the effects of heat and cold upon certain symptoms of multiple sclerosis. Bulletin of the Neurological Institute of New York 1937;6:385-6.
13. Guthrie TC. Visual and motor changes in patients with multiple sclerosis: a result of induced changes in environmental temperature. Arch Neurol 1951;65:437-51.
14. Davis FA, Schauf CL. Pathophysiology of multiple sclerosis. In: Davidson AN, Humphrey JH, Liversedge LA, et al. Multiple sclerosis research. London: HMSO, 1975:102-31.