

## **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]

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Received: 27 July 2003 / Accepted in revised form: 30 October 2003

**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

### 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  $\geq 24$  hours, without fever, accompanied by a new neurogenic abnormality, and preceded by stability or improvement for  $\geq 30$  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

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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.

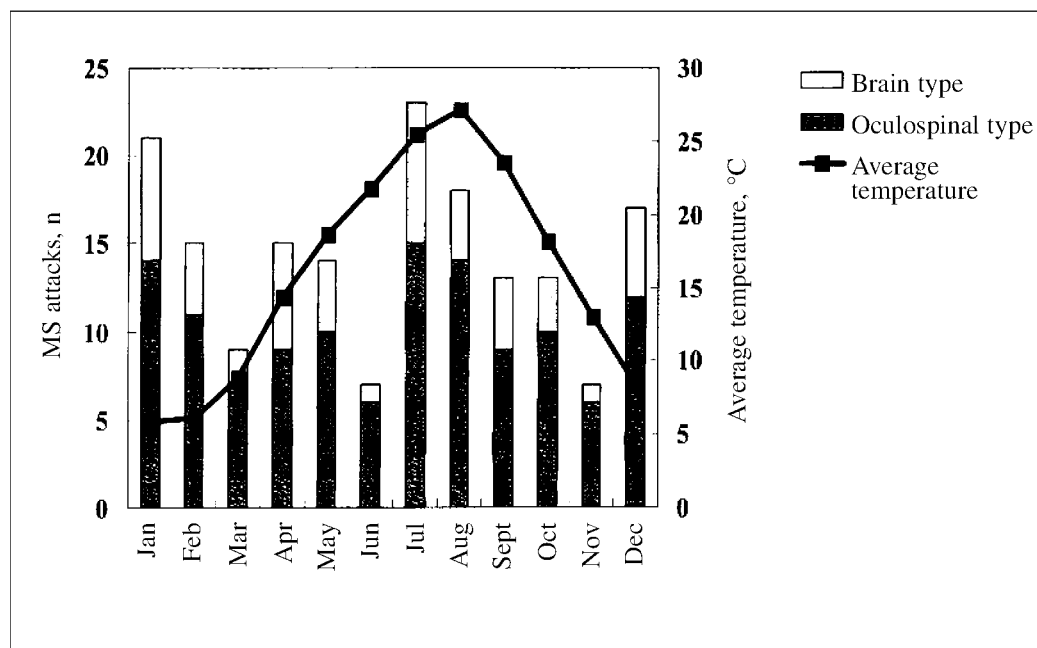
Statistical analysis was performed using the chi-square test.

## 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,  $\chi^2=18.57$ ,  $p>0.05$ ; opticospinal attacks,  $\chi^2=13.50$ ,  $p>0.05$ ; brain attacks,  $\chi^2=9.70$ ,  $p>0.05$ ).

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 ( $\chi^2=11.70$ ,  $p<0.05$ ); 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,  $\chi^2=4.51$ ,  $p>0.05$ ; opticospinal lesions,  $\chi^2=7.59$ ,  $p>0.05$ ).



**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

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## 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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