Climatic Influence on the Prevalence of Noncutaneous Disease Flare in Systemic Lupus Erythematosus in Hong Kong

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ABSTRACT. *Objective.* It is generally agreed that there is a seasonal variation in the prevalence of cutaneous manifestations of systemic lupus erythematosus (SLE). We investigated whether there is seasonal variation in the incidence of noncutaneous lupus flare in Hong Kong.

Methods. We reviewed all noncutaneous lupus flare in 222 consecutive patients with SLE followed in our clinic from 1995 to 2005. Specific organ involvement of each flare was reviewed. The variation in the prevalence of lupus flare by calendar month and the relation with climatic factors were determined.

Results. The total followup was 18,412 patient-months. In total, there were 313 episodes of noncutaneous flare recorded in 129 patients. There were more lupus flares in December and January [2.31 episodes, vs 1.58 episodes per 100 patient-months for other calendar months; relative risk (RR) 1.46, 95% CI 1.12–1.90, p = 0.004], and more flares of lupus nephritis in December and January (1.14 episodes, vs 0.60 episodes per 100 patient-months for other calendar months; RR 1.90, 95% CI 1.29–2.80, p = 0.001). There were more cases of membranous nephropathy in December and January (0.46 episode, vs 0.18 episode per 100 patient-months for other calendar months; RR 2.59, 95% CI 1.36–4.93, p = 0.0027), while the variation in prevalence of proliferative lupus nephritis was not statistically significant. There was also a significant U-shape correlation between the rate of lupus flare and the monthly average environmental temperature (r = 0.802, p = 0.0096), with higher flare rate at extremes of temperature.

Conclusion. We found substantial seasonal variation in the incidence of noncutaneous flare in our SLE patients, with peak incidence in December and January. There was a U-shaped relation between environmental temperature and the prevalence of noncutaneous flare. Keeping a warm living environment and avoiding exposure to extremes of temperature may help to reduce flare for SLE patients in subtropical countries. (First Release April 1 2008; J Rheumatol 2008;35:1031–7)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS   LUPUS NEPHRITIS   TEMPERATURE   HUMIDITY

Systemic lupus erythematosus (SLE) is a multisystem disease characterized by relapses and remissions. Photosensitivity, defined as reaction to sunlight resulting in the development of

or increase in rash, is a characteristic feature as well as one of the diagnostic criteria of SLE according to the American College of Rheumatology[1]. It is generally agreed that sunlight can aggravate cutaneous manifestations of SLE. Previous studies confirmed that flares of photosensitivity rashes in patients with SLE had a clear seasonality and occurred predominantly in the summer[2-4].

On the other hand, attempts to find a seasonal pattern for noncutaneous lupus disease flare were largely inconclusive. Investigations by Amit, *et al*[2] and Haga, *et al*[3] did not observe any seasonal variation in the prevalence of noncutaneous lupus activity. In contrast, Krause, *et al*[4] found that SLE patients have more joint pain in winter and spring, while Hasan, *et al*[5] noted that in the northern climate, SLE may be activated during the sunny seasons. In addition, Schlesinger, *et al*[6] observed that the prevalence of class V lupus nephritis was significantly higher in winter and spring. In a study from Puerto Rico[7], lupus patients that regularly used sunscreen had significantly lower renal involvement, thrombocytopenia, hospitalizations, and requirement for cyclophosphamide treat-

ment than other patients. Unfortunately, most of the published studies did not explore the role of other climatic factors in the risk of lupus flare.

We investigated whether there is seasonal variation in the incidence of noncutaneous lupus flare and examined possible contributing factors to such variability.

MATERIALS AND METHODS

Case selection. We reviewed 222 consecutive patients with SLE referred to the Combined Lupus Nephritis Clinic of the Department of Medicine and Therapeutics, Prince of Wales Hospital, from 1995 to 2005. All patients fulfilled the American College of Rheumatology (ACR) diagnostic criteria for SLE[1] and had history of significant proteinuria (24-hour urinary protein ≥ 1 g/day), with or without renal biopsy. The clinic was run every week throughout the year, except on statutory holidays, by 3 rheumatologists and 2 nephrologists; patients were as likely to attend in one month as the next.

Clinical management. During the study period, all patients were followed every 4 to 12 weeks as decided by the individual clinician. In addition, patients were advised to come to our weekly walk-in clinic whenever they had features of disease flare. In general, there are no prolonged typhoons or persistent heavy rain in Hong Kong that would delay patients from seeking early medical treatment. During each followup, serum electrolytes, urea, creatinine, albumin, liver enzymes, complements, and anti-double-stranded DNA antibody titers were measured. Lupus disease activity was assessed by the SLE Disease Activity Index (SLEDAI) score. Lupus flares were defined as one or more of the following[8-11]: > 3-point increase in SLEDAI score; or increase in prednisolone dosage. Renal flare is defined as one of the following[12,13]: (1) a reproducible (2 samples at least 1 week apart) increase in 24-hour urine protein levels to (a) > 1 g if the baseline value was < 0.2 g, (b) > 2 g if baseline value was 0.2 to 1 g, or (c) more than twice baseline if baseline value was > 1 g; (2) a reproducible increase in serum creatinine of > 20% or at least 25 μmol/l, whichever was greater, accompanied by proteinuria (> 1 g/24 h), hematuria [≥ 4 red blood cells (RBC)/hpf], and/or RBC casts; or (3) new, reproducible hematuria (≥ 10 RBC/hpf) or increase in hematuria by 2 grades compared with baseline, associated with > 25% dysmorphic RBC, exclusive of menses, accompanied by either an 0.8 g increase in 24-hour urinary protein levels or new RBC casts. Cerebral lupus was diagnosed according to the case definition system for central nervous system lupus syndromes by the ACR[14], including aseptic meningitis, cerebrovascular disease, demyelinating disease, lupus headache, movement disorder, myelopathy, seizure disorder, acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder, and psychosis. In this study, isolated cutaneous flares are excluded from the analysis. The date of disease flare is defined as the date that the patient first seeks medical advice and is validated by an independent third party.

During the study period, 313 episodes of noncutaneous lupus flare were recorded. Data on patient demographics, clinical features of the flare, and histological class of renal biopsy were reviewed.

Climatological information. The meteorological data used in this study were provided by the Hong Kong Observatory. We analyzed data on ambient temperature, net effective temperature (NET), relative humidity, and ultraviolet (UV) index. NET is a quantitative estimate of the common human perception to environmental temperature, and is calculated as follows[15,16]:

$$NET = 37 - \frac{37 - T}{0.68 - 0.0014 \times RH + 1/(1.76 + 1.4 \times v^{0.75})} - 0.29 \times T \times (1 - 0.01 \times RH)$$

where T is ambient temperature (centigrade), v is wind speed (m/s), and RH is relative humidity (%).

The ambient temperature, relative humidity, and wind speed data were recorded at the Shatin automatic weather station, located within the region of the study, while UV index data were recorded at the King's Park Meteorological Station in Kowloon, which is within 10 km from the area of this study.

Statistical analysis. Statistical analysis was performed by SPSS for Windows software version 11.5 and SigmaPlot software version 8.0 (both SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered statistically significant. All probabilities were 2-tailed.

We tested the assumption that the incidence of lupus flare would be constant throughout the study period by comparing the "expected" (calculated from the overall rate of lupus flare) and observed number of flares for each calendar month using the chi-square goodness-of-fit test. To determine further the extent of variability in the rate of lupus flare, we used the same test to directly compare flare rates for those months associated with the highest values relative to the overall incidence observed. The comparative risk of an incidence rate occurring in these months was then stated as relative risk (RR), 95% confidence interval (95% CI). Since a simple scatterplot of our data showed that the relation between the prevalence of lupus flare and various climatic factors may not be linear, correlation analyses explored by both linear and quadratic regressions were performed and the model with a higher correlation coefficient was chosen.

RESULTS

From 1995 to 2005, 222 patients with SLE were under the care of the Combined Lupus Nephritis Clinic in our center. Baseline clinical and demographic data are summarized in Table 1. The total duration of followup was 18,412 patient-months. During this period, a total of 313 episodes of noncutaneous lupus flare were recorded in 129 patients, with average SLEDAI score 10.3 ± 5.2 during the flare. The overall rate of lupus flare was 1.70 episodes per 100 patient-months. The clinical features of the lupus flares are summarized in Table 2. Of 127 episodes of renal flare, 74 episodes (58.3%) had kidney biopsy performed; 33 cases showed proliferative nephritis (WHO class III or IV), 25 showed pure membranous nephropathy (WHO class V), while 16 had mixed proliferative and membranous features.

Overall seasonal variation in flare rate. The average temperature of each month and the overall flare rate of each calendar month between 1995 and 2005 are summarized in Figure 1. There were more lupus flares in December and January (2.31 episodes, vs 1.58 episodes per 100 patient-months for other

Table 1. Baseline demographic and clinical data.

Characteristic	
No. of patients	222
Sex (M:F)	17:205
Age, yrs	31.1 ± 11.1
Hemoglobin, g/dl	11.5 ± 1.9
Platelets, × 10⁹/l	225.9 ± 79.5
White blood cell count, × 10⁹/l	6.0 ± 2.3
Serum creatinine, μmol/l	102.5 ± 71.3
Urine protein, g/day	1.48 ± 1.50
Estimated GFR, ml/min/1.73m²	96.8 ± 44.4
Serum albumin, g/l	32.4 ± 6.7
Serum C3, g/l	0.749 ± 0.280
Serum C4, g/l	0.174 ± 0.101
Anti-ds-DNA titer	276.4 ± 822.0
SLEDAI score	2.2 ± 2.0

Anti-ds-DNA: anti-double-stranded DNA antibody; SLEDAI: SLE Disease Activity Index.

Table 2. Clinical and histological features of lupus flare.

Feature	No. of Episodes	Rate of Flare (per 100 patient-months)
All flare	313	1.70
Nephritis	127	0.69
Non-renal flare	177	0.96
Cerebral lupus	14	0.08
Arthritis	130	0.71
Serositis	68	0.37
Hematological	124	0.67

calendar months; RR 1.46, 95% CI 1.12–1.90, p = 0.004). Although the median flare rate appeared to be static in July and August, the 75th and 90th percentile of flare rate were appreciably higher in July and August (1.84 episodes, vs 1.49 episodes per 100 patient-months for other calendar months; RR 1.24, 95% CI 0.86–1.62, p = 0.22), but the difference was not statistically significant.

The rate of flares of individual organ systems was analyzed further (Figure 2). There was a significant variation in the rate of lupus nephritis (overall chi-square test, p = 0.02). There were more flares of lupus nephritis in December and January (1.14 episodes, vs 0.60 episodes per 100 patient-months for other calendar months; RR 1.90, 95% CI 1.29–2.80, p = 0.001). Although there appeared to be another peak of nephritis flare in July and August (Figure 2A), the difference did not reach statistical significance. Similarly, the rates of extra-renal flare, arthritis, and serositis also tended to be higher in January and February (Figure 2), but the differences did not reach statistical significance.

We then examined the histological pattern of lupus nephritis in each calendar month (Figure 3). There were more cases of membranous nephropathy in December and January (0.46 episode, vs 0.18 episode per 100 patient-months for other calendar months; RR 2.59, 95% CI 1.36–4.93, p = 0.0027). In contrast, there were only marginally more cases of prolifera-
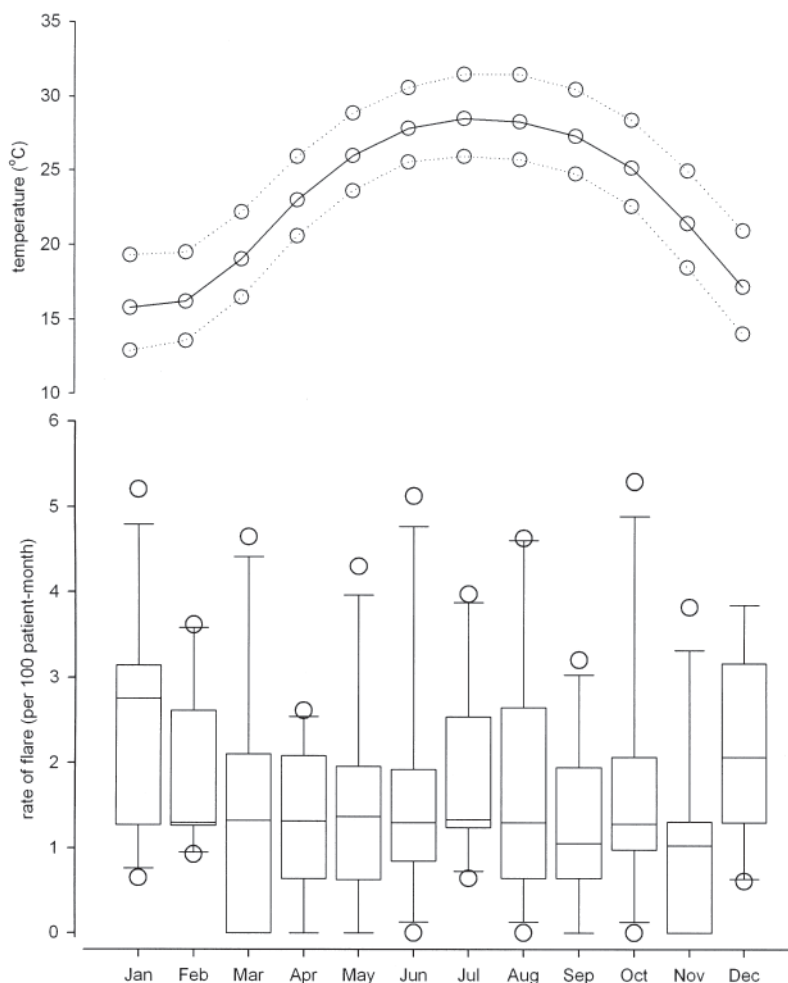

Figure 1. Average temperature of each month and the overall lupus flare rate for each calendar month from 1995 to 2005. In the temperature chart, solid line denotes average temperature of the month; broken lines denote maximum and minimum temperatures of the month. Boxes indicate median, 25th and 75th percentile rate of flare in each month during the 11 years; extensions indicate 5th and 95th percentiles.
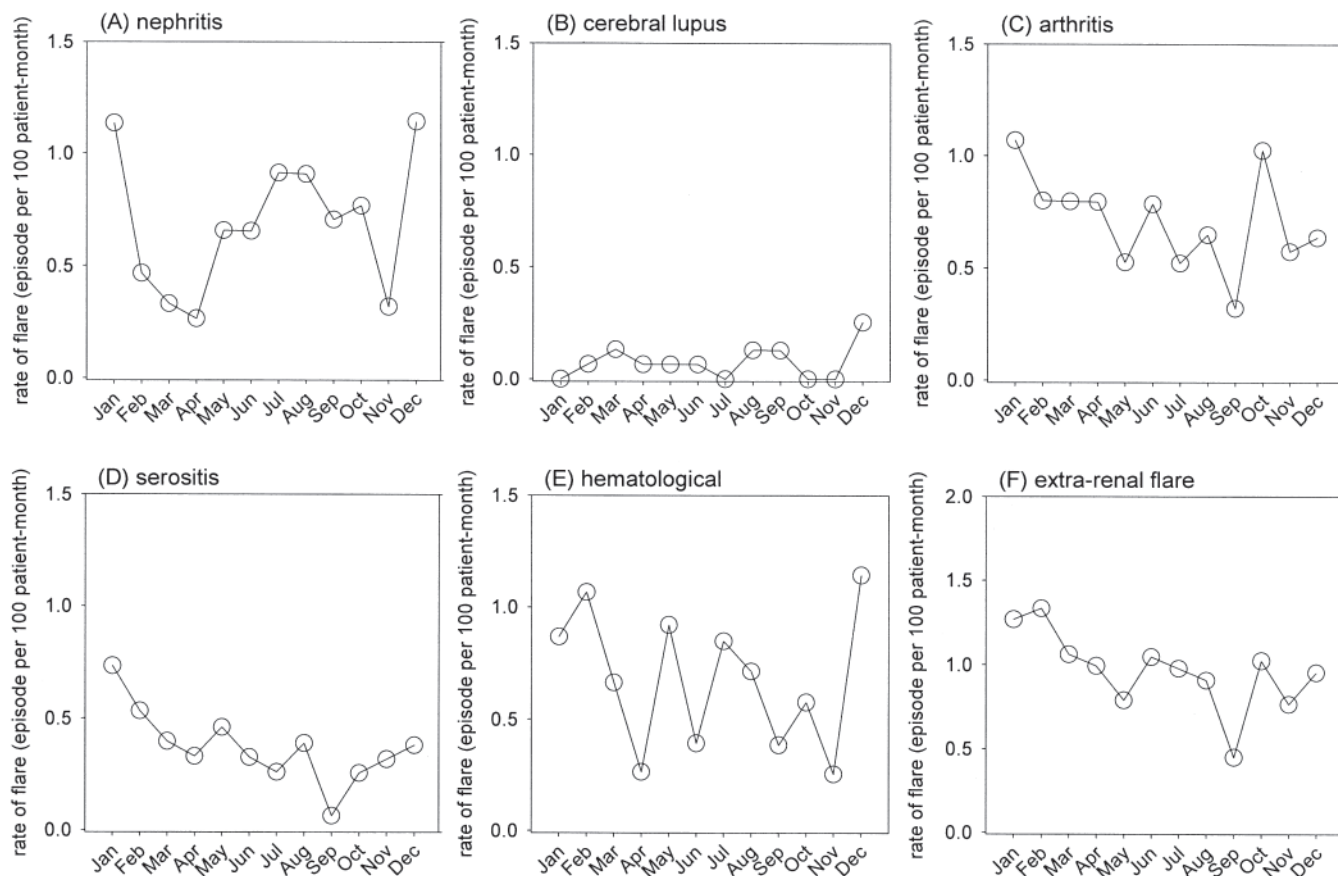
Figure 2. The rates of lupus flare within various organ systems: (A) nephritis, (B) cerebral lupus, (C) arthritis, (D) serositis, (E) hematological, and (F) any non-renal flare for each calendar month during the study period.
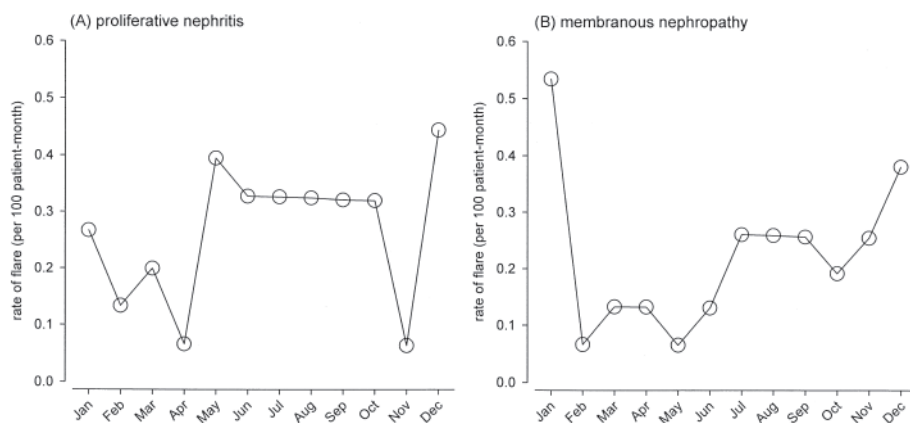

Figure 3. Rates of (A) proliferative lupus nephritis (WHO class III or IV) and (B) membranous lupus nephritis (WHO class V) for each calendar month 1995 to 2005.

tive lupus nephritis in December and January (0.36 episode, vs 0.25 episode per 100 patient-months for other calendar months; p = 0.28), but the result was not statistically significant.

Relation with climatic factors. During the 11-year study period, the average monthly temperature was 23.0 ± 4.9°C, aver-age monthly NET 18.8 ± 5.7°C, average monthly humidity 78.5% ± 4.9%, and average UV index 2.48 ± 0.72. The rate of lupus flare for each calendar month was plotted against the corresponding mean value of the following meteorological elements for that calendar month from 1995 to 2005 (Figure 4). As shown in Figure 4, there was a significant U-shape cor-
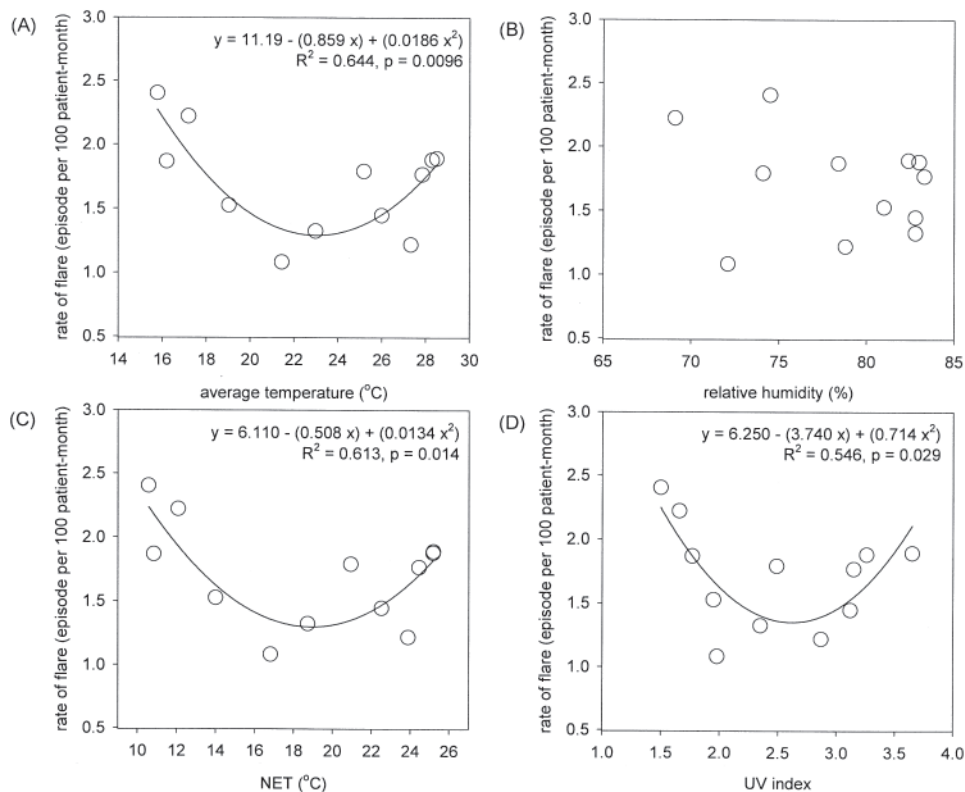
Figure 4. Relation between overall rate of lupus flare and the mean values of (A) monthly average temperature; (B) monthly average humidity; (C) monthly average net effective temperature (NET); and (D) monthly average ultraviolet (UV) index of each calendar month 1995 to 2005.

relation between the rate of lupus flare and the monthly average temperature (r = 0.802, p = 0.0096), NET (r = 0.783, p = 0.014), and UV index (r = 0.739, p = 0.029). On the other hand, there was no apparent relation between monthly average humidity and the rate of flare (Figure 4B).

Similarly, we further investigated the relation between monthly average temperature and the rate of flare of individual organ systems; the result is summarized in Figure 5. There was a U-shape correlation between monthly average temperature and hematological disease (r = 0.701, p = 0.048) as well as lupus nephritis (r = 0.683, p = 0.059), although the latter was not statistically significant. We also observed an inverse linear correlation between monthly average temperature and serositis (r = 0.663, p = 0.012), extra-renal flare (r = 0.574, p = 0.051), and arthritis (r = 0.472, p = 0.12), but the latter 2 did not reach statistical significance. Since the correlation between average temperature and rate of nephritis flare did not reach statistical significance, we did not further analyze the relation of average temperature and the rate of specific histological patterns of lupus nephritis.

DISCUSSION

In this retrospective study, we found substantial seasonal variation in the incidence of noncutaneous flare in our patients with SLE, with peak incidence in December and January.

There was a U-shaped relation between environmental temperature and risk of flare, and the seasonal variation was particularly marked for renal disease.

In brief, we found that renal and hematological diseases were more prevalent at the extremes of environmental temperature, while arthritis and serositis tended to be common only in cold weather (Figure 5). Our results are similar to those reported by Krause, *et al*[4], who found that SLE patients had more joint pain in winter and spring. In contrast to cutaneous problems[2-4], we found a quadratic relationship between UV index and the prevalence of noncutaneous flare (Figure 4), which is likely because the UV index is closely related to ambient temperature in Hong Kong. (During the study period, the correlation coefficient between monthly environmental temperature and UV index was 0.717; p < 0.0001.) Indeed, we believe UV exposure has very little effect on our patients because of our extensive program of patient education to avoid sunlight. Although the UV index is high throughout the year in Hong Kong, nearly all our patients had been advised to avoid outdoor activity and use sunscreen. The advice is well observed by most patients because the detrimental cosmetic effect is immediately obvious after sunlight exposure.

Similarly to Schlesinger, *et al*[6], we found that the prevalence of class V lupus nephritis was higher in winter months. The mechanism of this fluctuation remains obscure. Previous
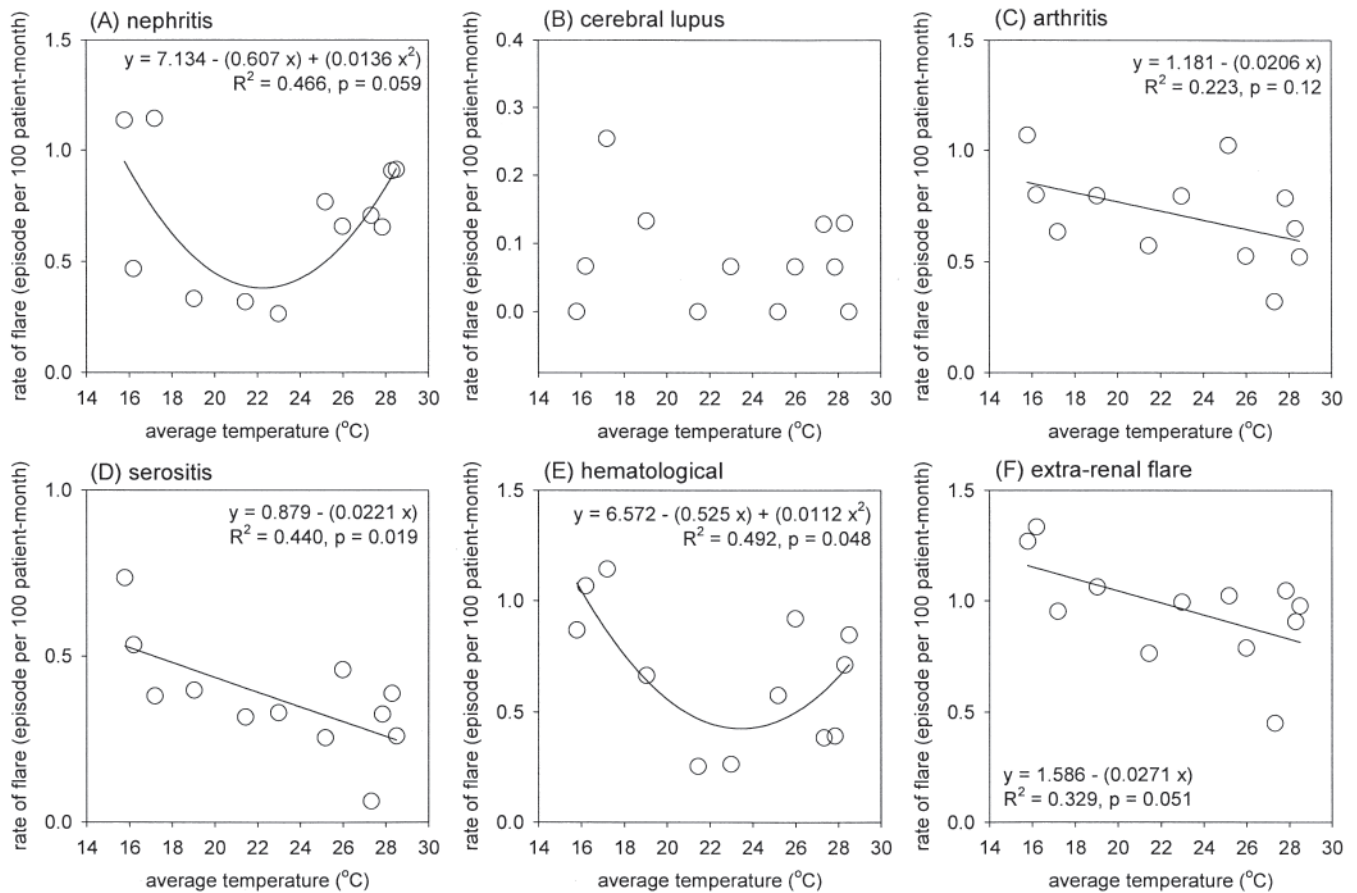
Figure 5. Relation between average temperature for each calendar month during the study period and rate of flare of organ systems: (A) nephritis, (B) cerebral lupus, (C) arthritis, (D) serositis, (E) hematological, and (F) any non-renal flare.

studies showed that there are seasonal variations in many autoantibodies[17-19]. It has also been suggested that the high prevalence of class V lupus nephritis during winter and spring may be a result of precipitating events such as infection or reactivation of endogenous retrovirus[6]. Alternatively, there could be an inherent seasonal fluctuation in the activity of the immune system[20]. For example, the number of circulating lymphocytes undergoes seasonal changes, reaching a peak in the winter months[21].

For practical convenience, we adopted a relatively generic definition of flare in this study. There is, however, no generally accepted single definition of lupus flare, and various definitions can be found[10,11]. Although the definition we used was largely objective, possible inaccuracies remain in the record of specific organ-system involvement for individual flare. Since the date of disease flare was defined as the date that the patient first sought medical advice, this could lead to substantial bias as some patients might decide to come weeks later, especially in cases of mild flares. It was also possible that a subset of patients (for example, those with minor nonrenal flares) might not seek any medical advice, resulting in bias in our record. This may also explain why the overall rate of lupus flare seems low in our patient population. Although our clinic was jointly run by rheumatologists and nephrologists, and we tried to avoid inadvertent emphasis on the renal aspect of the disease, it remains possible that there might have been bias in collecting data related to kidney involvement.

We did not examine cutaneous flare because of practical difficulties. It is difficult to distinguish transient photosensitivity reaction from genuine cutaneous flare in a retrospective study. More importantly, our record of cutaneous flare was incomplete because many of our patients did not seek medical advice for pure cutaneous flare. At any rate, published studies clearly demonstrated a seasonal variation in the incidence of photosensitivity rashes in patients with SLE[2-4].

We analyzed the effect of measured environmental temperature as well as net effective temperature (NET). The latter represents common human perception of hot and cold. NET is relatively simple to compute and easy to interpret. A large positive value implies exceptionally high heat load, while a large negative value represents large heat loss. In hot weather, NET increases as temperature and/or humidity increases, but decreases with increasing winds, while in cold weather, NET decreases with temperature, and with increasing humidity and

winds[15,16]. It should be noted that the rate of lupus flare correlated more closely with measured temperature than with NET (Figure 4), suggesting that the relation was a direct physical effect of environmental temperature but not of subjective human perception. It should be noted that we did not analyze a number of other meteorological or environmental factors. For example, atmospheric pressure, wind speed, rainfall, air pollution index, and the year to year climatic variation due to the El Nino phenomenon were not considered. Notably, air pollution and the El Nino phenomenon are well known to correlate with asthmatic attack and outbreak of certain infectious diseases, respectively[22,23]. Their influence on the prevalence of lupus flare would require further study.

ACKNOWLEDGMENT

REFERENCES

1. Hochberg M. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725-34.
2. Amit M, Molad Y, Kiss S, Wysenbeek AJ. Seasonal variations in manifestations and activity of systemic lupus erythematosus. Br J Rheumatol 1997;36:449-52.
3. Haga HJ, Brun JG, Rekvig OP, Wetterberg L. Seasonal variations in activity of systemic lupus erythematosus in a subarctic region. Lupus 1999;8:269-73.
4. Krause I, Shraga I, Molad Y, Guedj D, Weinberger A. Seasons of the year and activity of SLE and Behcet's disease. Scand J Rheumatol 1997;26:435-9.
5. Hasan T, Pertovaara M, Yli-Kerttula U, Luukkaala T, Korpela M. Seasonal variation of disease activity of systemic lupus erythematosus in Finland: a 1 year follow up study. Ann Rheum Dis 2004;63:1498-500.
6. Schlesinger N, Schlesinger M, Seshan SV. Seasonal variation of lupus nephritis: high prevalence of class V lupus nephritis during the winter and spring. J Rheumatol 2005;32:1053-7.
7. Vila LM, Mayor AM, Valentin AH, et al. Association of sunlight exposure and photoprotection measures with clinical outcome in systemic lupus erythematosus. PR Health Sci J 1999;18:89-94.
8. Buyon JP, Petri MA, Kim MY, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Ann Intern Med 2005;142:953-62.
9. Chan RW, Lai FM, Li EK, et al. Expression of T-bet, a type 1 T-helper cell transcription factor, in the urinary sediment of lupus patients predicts disease flare. Rheumatology Oxford 2007;46:44-8.
10. Petri M, Genovese M, Engle E, Hochberg M. Definition, incidence, and clinical description of flare in systemic lupus erythematosus: a prospective cohort study. Arthritis Rheum 1991;34:937-44.
11. Schiffenbauer J, Simon LS. Randomized controlled trials in systemic lupus erythematosus: what has been done and what do we need to do? Lupus 2004;13:398-405.
12. Linnik MD, Hu JZ, Heilbrunn KR, Strand V, Hurley FL, Joh T. Relationship between anti-double-stranded DNA antibodies and exacerbation of renal disease in patients with systemic lupus erythematosus. Arthritis Rheum 2005;52:1129-37.
13. Alarcon-Segovia D, Tumlin JA, Furie RA, et al. LJP 394 for the prevention of renal flare in patients with systemic lupus erythematosus: results from a randomized, double-blind, placebo-controlled study. Arthritis Rheum 2003;48:442-54.
14. American College of Rheumatology. Nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999;42:599-608.
15. Hentschel G. A human biometeorology classification of climate for large and local scales. In: Proceedings WMO/HMO/UNEP Symposium on Climate and Human Health, Leningrad, 1986. Geneva: Volume I, WMO-WCAP, No. 1:120-36.
16. Li PW, Chan ST. Application of a weather stress index for alerting the public to stressful weather in Hong Kong. Meteorological Applications, Vol. 7, Hong Kong Observatory, 2000:369-75.
17. Leff RL, Burgess SH, Miller FW, et al. Distinct seasonal patterns in the onset of adult idiopathic inflammatory myopathy in patients with anti-Jo-1 and anti-signal recognition particle autoantibodies. Arthritis Rheum 1991;34:1391-6.
18. Samuelsson U, Ludvigsson J, Bottazzo GF, et al. Islet cell surface antibodies are more common in patients and relatives in areas and during seasons with high incidence of insulin-dependent diabetes mellitus. Pediatr Res 1996;40:695-701.
19. Mikulecky M, Michalkova D. Secular and seasonal cycling of IA2-ab autoantibody in Slovak diabetic children. Biomed Pharmacother 2001;55 Suppl:106s-109s.
20. Boctor FN, Charmy RA, Cooper EL. Seasonal differences in the rhythmicity of human male and female lymphocyte blastogenic responses. Immunol Invest 1989;18:775-84.
21. Maes M, Stevens W, Scharpe S, et al. Seasonal variation in peripheral blood leukocyte subsets and in serum interleukin-6, and soluble interleukin-2 and -6 receptor concentrations in normal volunteers. Experientia 1994;50:821-9.
22. Tatum AJ, Shapiro GG. The effects of outdoor air pollution and tobacco smoke on asthma. Immunol Allergy Clin North Am 2005;25:15-30.
23. Kovats RS, Bouma MJ, Hajat S, Worrall E, Haines A. El Nino and health. Lancet 2003;362:1481-9.