Seasonal distribution of relapse onset in rheumatoid arthritis and spondyloarthropathy: The possible effect of the solar factor

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Abstract

Background and objective

The seasonal effect on the relapse of rheumatoid arthritis and spondyloarthropathies is still unclear. To assess the seasonal distribution of relapse onset in rheumatoid arthritis (RA) and spondyloarthropathy (SpA) and its association with solar factors.

Methods

The monthly distribution of relapse onsets during the years 1998 – 2000 was retrospectively chart reviewed in 364 patients. In 1998 a total of 131 patients were studied; 60 with seropositive (sp) RA, 30 with seronegative (sn) RA and 41 with SpA; 113 patients in 1999: 44 with spRA, 38 with snRA and 31 with SpA; 120 patients in 2000: 56 with spRA, 38 with snRA and 26 with SpA. All of them were treated in the Department of Rheumatology, which serves the population of northwestern Israel. Solar activity was analyzed according to the "Solar Terrestrial Activity Report Charts 1998-2000". The Central Israel Bureau of Statistics provided the sun global radiation data. Data was assessed during the summer (April-September) and winter (January-March, October-December). The correlation between the monthly distribution of disease relapses and solar factors was measured (SPSS-10 for WIN).

Results

Relapses in spRA patients occurred mostly during the summer months with peak activity during the month of July 2000. Single monthly peaks of spRA relapse onset were noted in January 1998-1999 and April 1998 and for snRA in January 1998 and June 2000, but there were no seasonal differences for spRA, snRA and SpA in 1998-1999 and for snRA and SpA in 2000. Relapses in spRA patients were associated with a summer bias of increased solar activity and global solar radiation in 2000 compared with lower peak solar activity in 1998-1999. Furthermore, in 2000 we found a significant correlation of the spRA monthly relapse count to solar activity ($p = 0.005$) and global sun radiation ($p = 0.048$) unlike snRA and SpA. No above-mentioned association and correlation was noted in 1998-1999. We revealed mild negative correlation ($p = 0.046$) of SpA relapse count only to peak solar flux (PSF) by analysis of data for 1998-2000 as one united group.

Conclusions

Relapses were more frequent during the summer of 2000 (May-June-July) in spRA but not in snRA and SpA. The reasons are still unclear. No seasonal differences were observed in 1998-1999. Enhanced solar activity in summer-2000 compared with 1998-1999 may be inferred to be the proposed cause but coincidence may occur as well. Outbreak in RA and SpA was not registered despite increased peak solar activity in 2000. We observed mild evidence of reciprocal relation between SpA relapsing and solar activity during 1998-2000. Solar and any other possible contributory factors remain still to be elucidated.

Key words

Seasonal distribution, relapse onset, rheumatoid arthritis, spondyloarthropathy, solar activity.

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Introduction

There is a popular belief that rheumatic conditions are particularly sensitive to fluctuations weather or outdoor temperature (1). Despite the possible influence of local heat on joint pains, the link between the season and pain in rheumatic diseases appears difficult to prove (2, 3).

Previous studies in women with rheumatoid arthritis (RA) conducted in Australia have shown an association of pain and stiffness with increasing humidity and decreasing temperature (3). RA patients often report a link of pain and stiffness with cold temperature, changes in humidity, and following high barometric pressure, but the relationship is not clinically significant (4). A retrospective study of the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) concentration of 2802 RA patients (Southwestern Oklahoma, 1970-78) has found no statistically significant fluctuation when analyzed according to the month of the year in which blood was drawn (5). Even though common opinion is that heat acts as palliative and cold is stressful factor, the authors conclude that seasons and climate may affect some of the symptoms of RA but not the inflammatory process. Compared with a seasonal summer pattern in the onset of polymyalgia rheumatica the onset of symptoms in elderly onset RA patients was scattered throughout the year with no seasonal clustering in Italian study (Genoa) (6). Across Canada the onset of systemic-onset juvenile rheumatoid arthritis was also constant across seasons with the exception of one region with peaks in autumn and early spring (7).

On the other hand, there is data in the northern hemisphere, where the onset of RA from October to March was found to be twice as frequent as in the other months (8). Furthermore, in cohort of 106 ankylosing spondylitis patients lumbar spine flexibility and quality of life improved in the summer and deteriorated during the cold season (1).

Seasonal variation in systemic onset juvenile rheumatoid arthritis (SOJRA) was followed in Israel from 1982 to 1997 (9). A seasonal pattern to SOJRA disease onset was not found. However, the disease onset of patients having the chronic or the polycyclic subtype, which is the more severe disease, tended to be more common in winter and spring, but the monophasic subtype was observed twice as frequently in the summer. The authors hypothesized that a seasonal peak onset of subtypes of SOJRA may be suggestive of an infectious etiology (9).

Despite the above-mentioned trials, we decided to investigate the timing of arthritis relapse onset and solar activity again for several reasons. There is a possible influence of a change in solar activity and a possible new deviation of solar activity. It has been proposed that local (latitude) and regional (Mediterranean basin) factors may also have an influence. No study has been performed in our region for RA and spondyloarthropathy. The possible interaction of solar activity with new variations in background origin (medications, infection) is to be elucidated.

We present data of the seasonal distribution of relapse onset in adult RA and spondyloarthropathy (SpA) and its association with solar factors in 1998-2000 that have not been previously investigated in Israel.

Methods

The monthly distribution of the relapse onset during the years 1998-2000 was retrospectively chart reviewed in 364 patients: 131 in 1998 comprising 60 with seropositive (sp) RA, 30 with seronegative (sn) RA and 41 with SpA; 113 patients in 1999 comprising 44 with spRA, 38 with snRA, and 31 with SpA; and 120 patients in 2000 which included 56 with spRA, 38 with snRA and 26 with SpA. The relapse count is presented in Table I and its monthly distribution is depicted in Fig. 1 a-c. All of them were treated in the Department of Rheumatology, which serves the population of Northwest Israel. The onset of RA relapse was defined according to the month of appearance of symmetric pain and swelling of three or more joint areas involving at

Table I. The distribution of RA and SpA relapses, assessment of joint and spine inflammation activity with DAS 28 and BASDAI scores during onset of relapse and current therapy (1998-2000).

Disease	No. of relapses in 1998	1999	2000	Total no. of relapses 1998-2000	Average DAS 28 (Active RA > 5.1)	Average BASDAI	MTX 1998-2000 %	SSZ	Plq	NSAID	Gold	Imuran	Minocin	PNCLA	CS 2.5-10 mg/d
sp RA	64	47	59	170	7.2 ± 1.1		48	19	23	38	5	3	2	2	38
							51	17	26	45	6	4	4	6	41
							42	14	20	47	3	0	0	3	46
snRA	33	39	40	112	6.6 ± 0.9		30	21	18	24	0	0	3	3	24
							28	24	10	41	3	3	7	0	21
							18	18	8	53	0	0	0	0	15
SpA	41	31	26	98	-	5.8 ± 0.8	10	20	0	46	2	5	2	0	7
							6	26		65	0	3	4		12
							0	12		77	0	4	0		15
AS	14	9	10	33	-	6.3 ± 1.2	0	10	0	90	0	6	0	0	6
PsA	12	10	11	33	-	5.6 ± 0.7	12	18	0	45	3	3	0	0	6
IBD	4	5	3	12	-	6.1 ± 1.4	0	75	0	17	0	8	17	0	50
ReA	5	4	1	10	-	5.7 ± 0.5	0	0	0	50	0	0	0	0	0
Undif SpA	6	3	1	10	-	6.8 ± 1.7	20	10	0	70	10	0	0	0	10
Total	138	117	125	380											

spRA: seropositive RA; snRA: seronegative RA; SpA: spondyloarthropathy; AS: ankylosing spondylitis; PsA: psoriatic arthropathy; IBD: inflammatory bowel disease; ReA: reactive arthritis; Undif SpA; undifferentiated SpA; DAS:Disease Activity Score index; BASDAI:Bath Ankylosing Spondylitis Disease Activity Index; MTX: % of patients treated with methotrexate during relapse; SSZ: % treated with sulfasalazine; Plq: plaquenil (hydroxychloroquine); PNCLA: penicillamine; CS: corticosteroids.

least one swollen joint area in the wrist, MCP or PIP joints with morning stiffness lasting at least 1 hour before maximal improvement (revised ARA Criteria 1988). The disease activity score with three variables (DAS28) assessed the disease activity and patients were recorded to have a relapse when DAS28 was above 5.1 (10) (Table I). The month of appearance or exacerbation of inflammatory back pain, spinal stiffness and/or peripheral joint/entheses involvement with BASDAI (11) and a BASFI (12) score above 5.0 (or a rise in the indices above 1.0) was assessed as the onset of relapse in the SpA group (Table I). Spine pains were considered inflammatory when they were insidious at onset, improved with exercise, were not relieved by rest and were associated with morning stiffness. SpA was diagnosed in patients with inflammatory spine pain, active sacroiliitis and/or asymmetric synovitis in the lower limbs with any one of the following: a positive family history, psoriasis, inflammatory bowel disease, or alternate buttock pain and enthesopathy (ESSG Criteria 1991). All cases in which any changes in treatment had taken place during at least the last 8 months were excluded from the score.

Solar activity was analyzed according to the "Solar Terrestrial Activity Report Chart 1998-2000"(www. dxlc.com/solar/) and included an estimation of three main parameters: solar flux, sunspot number and planetary A index (Fig. 2 a-c). Solar flux (SF) is the outward flow of solar particles and magnetic fields from the sun measured per unit of section surface. Typically, solar flux (wind) velocities are near 350 km/s. A sunspot is an area which appears as a dark spot on the photosphere of the sun. Sunspots are concentrations of magnetic flux, typically occurring in bipolar clusters or groups. They appear dark because they are cooler than the surrounding photosphere. The sunspot number (SN) is a daily index of sunspot activity ®, defined as R = k (10g + s) where s = number of individual spots, g = number of sunspot groups, and k is an observatory factor. The planetary A index (PAI) represents the average daily geomagnetic activity measured by a set of specific stations. PAI and its related indices (Kp, ap, Cp) have been widely used in ionospheric and atmospheric studies and are generally recognized as indices measuring the effect of energetic charged particles entering the earth's upper atmosphere after periods of intense solar activity. A worldwide disturbance of the earth's magnetic field, distinct from regular diurnal variations is called a "geomagnetic storm" (according to the SESC Glossary of Solar-Terrestrial Terms, DOC/NOAA/ERL/SEL). We used monthly peaks of SF (PSF), SN (PSN) and PAI (PPAI) as values carrying maximal solar energy.

Because the three above-mentioned solar characteristics might provide an integral influence on humans we proposed an empiric integral index of the solar activity (IISA) which seems to be a relative biological equivalent of sun action. We defined IISA by the equation: IISA = (PSF + k_1 PSN + k_2 PPAI)/3, where k_1 and k_2 are unknown quotients of the fractional participation of

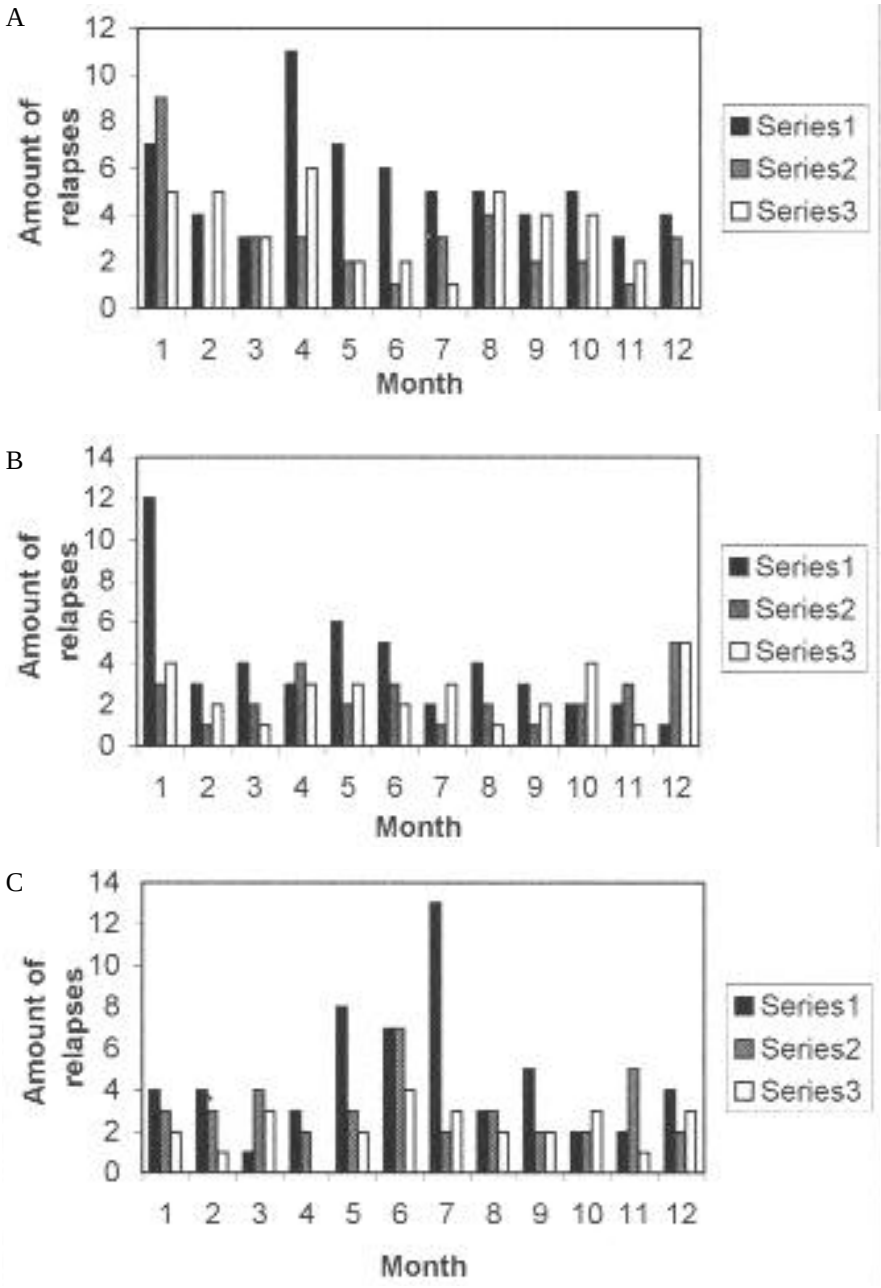

Fig. 1. Monthly distribution of seropositive RA (1); seronegative RA (2); and spondyloarthropathy (3) relapses in (**A**) 1998; (**B**) 1999; and (**C**) 2000.

SN and PAI in biological action. Although the real biological significance and value of these quotients remain to be clarified we conceded that these quotients might be taken as 1.0 according to the main energetic action of solar flux. The area under the curve squared (Fig. 2A-C) may be associated with the IISA value. IISA showed a good correlation to PSF during the years 1998-2000 years (0.81, 0.86 and 0.89 respectively, $p < 0.001$). Therefore we used values of IISA in the assessment of solar activity and the relapse-solar correlation along with PSF, SSN and PAI.

The Central Israel Bureau of Statistics provided the sun global radiation data measured on the earth's surface (solar radiation, Mjoule/m^2/d), daily temperature and sunshine time (13). The data was assessed during the summer (April - September) and winter (January-March, October-December) of 1998-2000 (Fig. 3). We should emphasize the need to distinguish solar activity as an independent sun characteristic and solar radiation (measured at the Beit-Dagan station) as the seasonal function. The statistical analyses were carried out using the SPSS-10 FOR WIN. Analyses of differences were performed using the Wilcoxon matched-pairs signed-ranks test and the Mann-Whitney U-Wilcoxon Rank Sum W Test. Correlation was performed using the Pearson correlation coefficient.

Results

The number of relapses for seropositive and seronegative RA and SpA in 1998-2000 is presented in Table I. The number of relapses of spRA, snRA and SpA was not higher in 2000 even if solar activity in 2000 showed much higher values when compared to 1998-1999 (Table IA-B). Single monthly peaks of spRA relapse onset were noted in January 1998-1999 and April 1998 and for snRA in January 1998 and June 2000, but there were no seasonal differences for spRA, snRA and SpA in 1998-1999 or for snRA and SpA in 2000 (Fig. 1 a-c). Relapses in spRA patients occurred mostly during the summer 2000 months (May-June-July) with peak activity during the month of July, compared with the equally distributed relapse onset of snRA and SpA between summer and winter (Table II, Fig. 1c). The relapse onset in spRA (Fig. 1c) was associated with a summer 2000 bias in solar activity (Fig. 2c: see similar May-July "stepwise" activity) and global solar radiation, daily temperature and monthly sunshine time curves (Table II, Fig. 3). This trend was not observed in spRA, snRA and SpA or in 1998-1999 (Fig. 1 a-b and Fig. 2 a-b, Table II). We found a significant correlation between the monthly spRA relapse count to solar activity ($p = 0.005$) and global sun radiation ($p = 0.048$) unlike snRA and SpA in 2000. No correlation of the monthly relapse count to solar activity was observed in 1998-1999 (Table III). We discovered a mild negative correlation ($p = 0.046$) of the SpA relapse count only with the peak solar flux (PSF) on analysis of the data for 1998-2000 as one united group (Table III A).

Monthly peak solar activity during 2000 was distinguishable from the two previous years by three important find-

Table I. (**A**) Paired monthly comparison of relapse count and peak solar activity between 2000 and 1998 – 1999.

spRA 2000 – 1998 p = 0.28	spRA 2000 – 1999 p = 0.44	snRA 2000 – 1998 p = 0.68	SnRA 2000 – 1999 p = 0.22
SpA 2000 – 1998 p = 0.11	SpA 2000 – 1999 p = 0.41	IISA 2000 – 1998 p = 0.002	IISA 2000 – 1999 p = 0.02
PSF 2000 – 1998 SSN 2000 – 1999 p = 0.002	PSF 2000 – 1999 p = 0.14	SSN 2000 – 1998 P = 0.002	P = 0.06
PAI 2000 – 1998 p = 0.56	PAI 2000 – 1999 P = 0.04		

Table I. (**B**) Non-paired (general annual group) comparison of relapse count and peak solar activity between 2000 and 1998 – 1999.

spRA 2000 – 1998 p = 0.24	spRA 2000 – 1999 p = 0.48	snRA 2000 – 1998 p = 0.37	snRA 2000 – 1999 p = 0.21
SpA2000 – 1998 p = 0.08	SpA 2000 – 1999 p = 0.51	IISA 2000 – 1998 p < 0.001	IISA 2000 – 1999 p = 0.02
PSF 2000 – 1998 p < 0.001	PSF 2000 – 1999 p = 0.17	SSN 2000 – 1998 p < 0.001	SSN 2000 – 1999 p = 0.03
PAI 2000 – 1998 p = 0.53	PAI 2000 – 1999 p = 0.08		

spRA: seropositive RA; snRA: seronegative RA; SpA: spondyloarthropathy; IISA: integral index of solar activity; PSF: peak solar flux; SSN: sunspots number; PAI: planetary A index.

Table II. Summer over winter predominance in the relapse counts in RA and SpA patients and solar activity and radiation in 1998-2000 (p).

	spRA	snRA	SpA	IISA	PSF	SSN	PAI	Solar radiation
1998	0.09	0.81	0.80	0.20	0.52	0.17	0.20	0.004
1999	0.37	0.51	0.62	0.57	0.69	0.74	0.42	0.004
2000	0.05	0.61	1.00	0.007	0.07	0.02	0.03	0.004

Table III. Annual correlation of spRA, snRA and SpA monthly relapse counts to solar activity and global sun radiation in 1998-2000.

Disease/year	Solar activity (IISA)	Solar radiation	PSF	SSN	PAI
spRA98	-0.18 (p = 0.58)	0.31 (p = 0.32)	-0.23 (p = 0.47)	-0.24 (p = 0.45)	-0.21 (p = 0.50)
snRA98	-0.21 (p = 0.51)	-0.24 (p = 0.45)	-0.19 (p = 0.55)	-0.40 (p = 0.20)	-0.14 (p = 0.67)
SpA98	-0.04 (p = 0.90)	-0.20 (p = 0.54)	-0.22 (p = 0.49)	-0.49 (p = 0.11)	0.07 (p = 0.84)
spRA99	-0.08 (p = 0.81)	-0.08 (p = 0.80)	0.14 (p = 0.67)	-0.13 (p = 0.69)	-0.27 (p = 0.39)
snRA99	-0.19 (p = 0.55)	-0.37 (p = 0.24)	0.03 (p = 0.92)	-0.13 (p = 0.68)	-0.45 (p = 0.14)
SpA99	-0.15 (p = 0.63)	-0.32 (p = 0.31)	-0.05 (p = 0.87)	-0.30 (p = 0.35)	0.10 (p = 0.77)
spRA2000	0.75 (p = 0.005)	0.58 (p = 0.048)	0.72 (p = 0.008)	0.67 (p = 0.017)	0.56 (p = 0.06)
snRA2000	-0.27 (p = 0.39)	0.17 (p = 0.59)	-0.22 (p = 0.49)	-0.16 (p = 0.62)	-0.29 (p = 0.36)
SpA2000	0.07 (p = 0.82)	0.24 (p = 0.45)	0.05 (p = 0.85)	0.11 (p = 0.73)	0.04 (p = 0.91)

Table III. (A) Correlation of spRA, snRA and SpA monthly relapse counts to solar activity and global sun radiation in 1998-2000 calculated as for one united group.

Disease in 1998-2000	Solar activity (IISA)	Solar radiation	PSF	SSN	PAI
spRA	0.13 (p = 0.44)	0.27 (p = 0.11)	-0.05 (p = 0.77)	-0.11 (p = 0.54)	-0.15 (p = 0.37)
snRA	-0.10 (p = 0.60)	-0.4 (p = 0.42)	-0.03 (p = 0.88)	-0.05 (p = 0.78)	-0.14 (p = 0.67)
SpA	-0.27 (p = 0.11)	-0.11 (p = 0.53)	-0.33 (p = 0.046)	-0.30 (p = 0.08)	-0.27 (p = 0.90)

Abbreviations:spRA – seropositive RA, snRA – seronegative RA, SpA – spondyloarthropathy, IISA – integral index of solar activity, PSF – peak solar flux, SSN – sunspots number, PAI – planetary A index.

ings (Fig. 2A-C, Fig. 4). First, the peaks of solar flux, sunspot number and planetary A index coincided and were registered during July, the month of the maximal appearance of spRA relapses. Second, two peaks of solar flux were close and separated by two months only, concentrating solar energy during the summer period compared with the three-month interval during the autumn in the previous two years. Third, the average value of solar flux, the carrier of maximal solar energy, was much more significant when compared to the years 1998 and 1999 (Fig. 4).

Discussion

The first mention of the possibility of a summer bias in the relapse of RA was reported in the Oklahoma Study (5). This study, performed in southwestern Oklahoma in 1970-1978, found no statistically significant monthly fluctuation in RA during this period. However, the authors highlighted the example of one year when the April-June elevation in the RA relapse count occurred with characteristic April-May-June "stair" in ESR dynamic that resembled May-June-July "stair" of spRA relapse shown in our study (Fig. 1c). Authors emphasized the need to secure large test groups when dealing with RA but at first the summer seasonal sample of

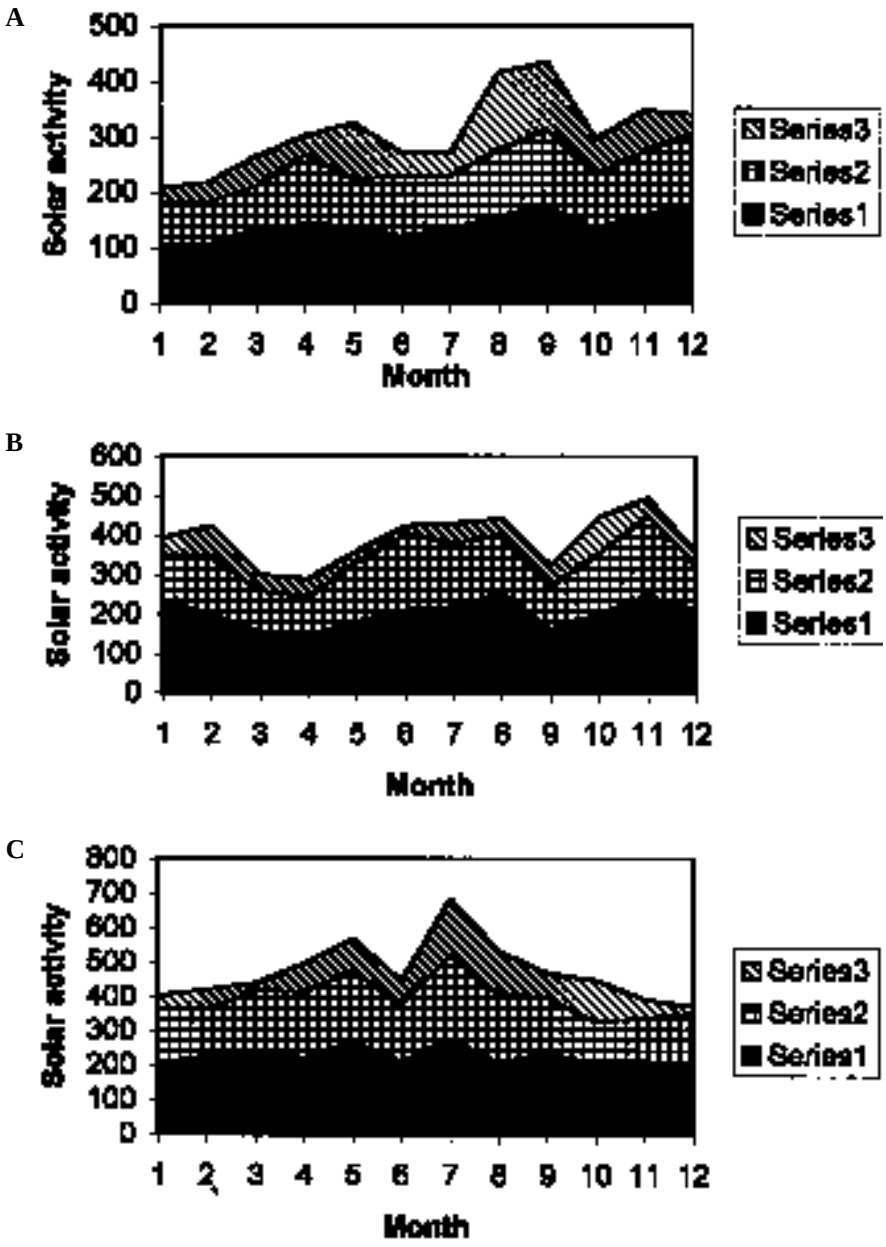

Fig. 2. Monthly peak solar flux (1); sunspot number (2); and planetary A index (3) in: (**A**) 1998; (**B**) 1999; and (**C**) 2000.

RA relapsing was registered just over one year. It is also necessary to provide large sample sizes not only in the number of subjects during a number of years but also in the number of measurement points.

The second indication for a certain subset of RA flare in summer was reported for juvenile rheumatoid arthritis with systemic onset that further developed as monophasic subtype, which was observed twice as frequently in summer (9). Authors considered unknown influence of infectious factor (9).

The possibility of summer clustering of polymyalgia rheumatica (PMR), the disease of cell-mediated autoimmunity as well as RA, has been well-documented (6). The monthly distribution of PMR correlated with the outside temperature and hours of sunshine. This data, reported for the Mediterranean Sea region (Italy), suggests that PMR might be triggered by such factors as actinic sun damage of the superficial vessels or infective agents with a seasonal cycle (6).

We found that relapses in spRA patients occurred mostly with statistical significance during the summer months of 2000 unlike snRA and SpA and when compared with the prior two years. However, the maximal number of relapses in snRA and SpA was also noticed in the summer month of June 2000. Single monthly peaks of spRA relapse onset were also noted in January 1998-1999 and April 1998 and for snRA in January 1998, but there were no seasonal differences. We observed a summer predominance of spRA and a summer trend of snRA and SpA flare in 2000. The reason for this is still unclear, although we would suggest several factors which may be responsible:

1) Solar activity 2000. The monthly peak solar activity during 2000 was distinguished from the data of the 2 previous years by the above-mentioned characteristics: a much higher solar flux value; the coincidence of PSF, PSN and PPAI in July; and the closer proximity of solar flux peaks providing a maximal concentration of solar energy during summer months (Fig. 2 a-c, Fig. 4).
2) Increased ultraviolet B/A ratio during the summer months. In addition to abnormally increased photosensitivity to ultraviolet radiation (UVR) exposure, photo-aggravation of systemic disease activity may occur in systemic lupus erythematosus (14). A preponderance of UVA over UVB was found, and was more strongly expressed at the Dead Sea, which increased with the approach of winter and decreased in the summer months, providing a severe UVB load during the summer (15). Whether the summer predominance of the UVB/UVA ratio may be responsible for the summer elevation in the cases of RA and SpA relapses remains to be confirmed. However, the propagation of solar activity in 2000 may have aggravated the UVB influence. Recently it was discovered that irradiation of human dermal microvascular endothelial cells with UVA1 or UVB enhanced the expression of proopiomelanocortin peptides such as alfa-melanocyte-

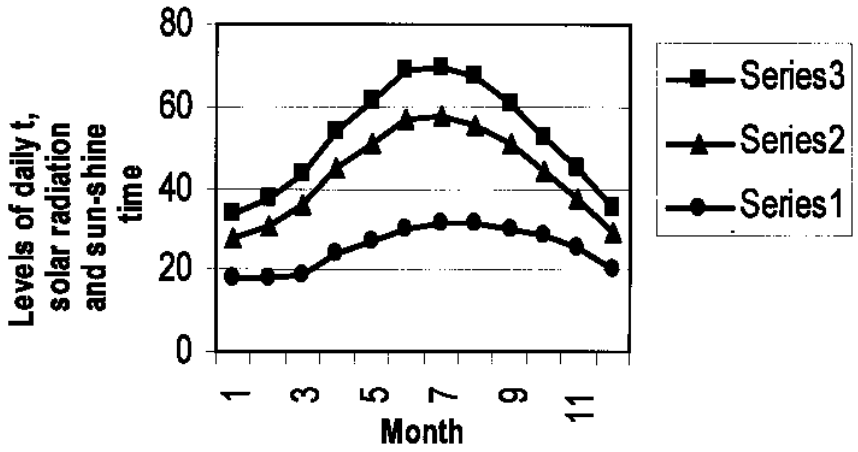

Fig. 3. Average monthly curves of daily temperature (1), solar radiation (2), and sunshine time (3) 1998-2000 (Beit-Dagan Station).

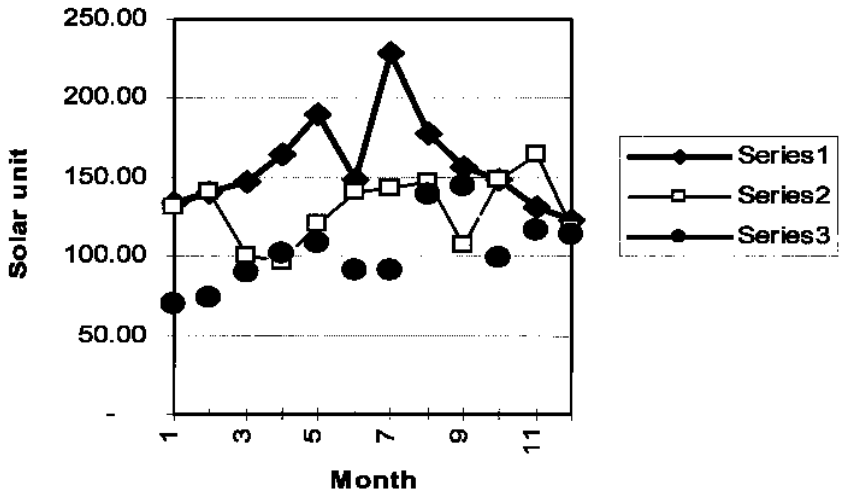

Fig. 4. Monthly peak solar activity (IISA) 1998-2000 (series 1: 2000, series 2: 1999, series 3: 1998). Monthly peak solar activity (IISA-integral index of solar activity) during 2000 was distinguished from 1998-1999 by important properties. The peaks of solar flux, sunspot number and planetary A index (composing IISA) coincided and were registered during July, the month of maximal appearance of spRA relapses. Second, two peaks of solar flux were close and separated by two months only, concentrating solar energy during summer period compared with three-month interval during autumn in previous two years. The average value for solar flux, a carrier of maximal solar energy, was much more significant when compared to 1998 and 1999.

stimulating hormone and adrenocorticotropin in the epidermal and dermal compartments of the skin (16). Its synthesis was upregulated by interleukin-1-beta. These peptides were found to regulate the production of human dermal microvascular endothelial cell cytokines and adhesion molecules, modulating the immune and inflammatory process (16). Another recent study demonstrated that cultured human keratinocytes were capable of producing interleukin-10 (IL-10) induced by UVB and, more vigorously, by UVA1 radiation (17). IL-10 is a severe anti-inflammatory cytokine with its capacity to suppress the production of interferon-gamma. We can suggest that increased UVB radiation during the summer may change the cytokine profile and promote inflammatory disease flare-ups. On the other hand, UVB radiation induces exaggerated keratinocyte apoptosis – a potential source of fragmented autoantigens due to DNA and cell damage, mediating autoimmunity in genetically susceptible organism (18).

3) Thermal effects and the overproduction of heat shock proteins (HSP) were related to infrared radiation, especially in the summer season at southern latitudes with extremely high temperatures. The proteins induced by heat (stress or heat shock proteins) appear to play a general role in protection from cellular injury and eventually in the natural defense from solar radiation (19). Immunity against HSPs might directly contribute to synovitis and joint destruction by involvement of T lymphocytes and such reactive T cells can transfer experimental arthritis. The critical step required to initiate RA would reside in the combination of an appropriate class II MHC haplotype and a pathogen that expresses cross-reactive HSPs (20). But there is conflicting data when decreased day temperatures are associated with both increased joint pain and increased joint rigidity and vice versa (3, 4, 21, 22). There is also data for the northern hemisphere showing that the onset of RA in winter was twice as frequent as in the summer (8). Therefore, relations between environmental temperature and RA and SpA flare-ups require further confirmation.
4) Effects of visible light that are dominant in the summer months. The pain – light season/dark season hypothesis was investigated in 2523 rheumatic disease outpatients by examining VAS Pain and VAS Global Severity scores, as well as levels of depression and functional disability in Wichita (USA) (23). No clinically significant difference in pain severity between the season and the individual month was noted. A slight trend toward increased pain severity in the lighter months by about 3% compared to the darker months was noted. In a subset of patients with a high depression score, rheumatoid arthritis and osteoarthritis patients, reported 16% and 7% greater pain scores in

the light compared to the dark months respectively (23).

5) Nucleotide pool activation during the summer season in T-lymphocytes of RA patients. Data from Italian authors (24) indicates the activation of the nucleotide pool (mostly monophosphates, unlike di- and triphosphates) in T-lymphocytes of RA patients during the summer period compared with healthy controls. Methotrexate was found to decrease the pool of serum purine and pyrimidine nucleotide metabolites (25). The data was attributed to a possible mechanism of the drug action, which may be associated with a decrease in the serum nucleotide precursors of lymphocyte proliferation and activation. The results of the Italian study may be relevant to countries in the Mediterranean basin with a similar climate.
6) Biological action of factors other than thermal and meteorological parameters, such as relative humidity, barometric pressure, wind speed and precipitation (21) and as yet unknown influences. An Australian study showed that increased relative humidity was associated with increased joint pain and rigidity in patients with RA and osteoarthritis (21). Correlation between these symptoms and relative humidity were significant ($p < 0.001$). Stepwise multiple regression analysis indicated that meteorological variables and the time of day accounted for 38% of the variance in mean pain and 20% of the variance in mean rigidity when data for all months was considered. A post-study telephone questionnaire indicated that 92% of participants perceived their symptoms to be influenced by the weather, and 48% claimed to be able to predict the weather according to their symptom (21). A Dutch study analyzing 88 patients with RA living in the marine climate of a coastal province scored their pain symptoms daily during a full year. The study indicated that RA pain significantly ($p < 0.01$) decreased with elevations of the vapor pressure and increased ($p < 0.02$) with elevations in the relative humidity (22). These correlations were stronger in the summer than in the winter. High summer humidity, reaching 70-80% along the northwestern coast of Israel, and vapor pressure fluctuations, may be significant affecting factors.
7) Seasonal use of chemical agents in agriculture as an explanation for the induction of new antigens, which may irritate the immune system and be a source of breakdowns in its function. We have no evidence of this hypothesis so far and it must still be elucidated.
8) Interaction of solar radiation with medications. Of our patients 50% were treated with methotrexate, 15-20% with Salazopyrine, 20% with Plaquenil and 40-50% with NSAIDs. Information regarding the interaction of sun radiation and methotrexate is lacking, but photosensitivity to sulfa-containing medications is well established. Whether this interaction may be responsible for inflammatory joint disease flare-ups is a subject for further research.
9) Seasonal fluctuations in lysosomal enzyme activity in the synovial fluid of RA patients. A study of the activity of 4 lysosomal enzymes (deoxyribonuclease, acid phosphotase, acid cathepsines and beta-galactosidase) in synovial fluid depending on the month was conducted in 112 patients with RA (26). A statistically significant chronobiological difference in this parameter was shown for all investigated enzymes, increasing in the spring and autumn and decreasing in the summer and winter. The significance of seasonal lysosomal activity fluctuation in the synovial fluid of patients with RA is still unclear.
10) Association with seasonal infections. A significant correlation of monthly relapses in snRA to the monthly distribution of UTI caused by *P. mirabilis* was recently reported (27). A solar–infection interaction may be implied.

When analyzing the seasonal distribution of rheumatic diseases according to the influence of solar factors we should take into account the latitude of region being considered. The closer it is to the equator, the smaller the difference between summer and winter radiation. For instance, the ration of insolation between June and January is 20 in southern Sweden and only 5 in Belgium. Consequently, the radiation load in southern countries is much higher than in the north.

In conclusion, relapses were more frequent during the summer of 2000 in spRA but not in snRA and SpA and no seasonal predominance was observed in 1998-1999 for all three diseases. Enhanced solar activity in the summer of 2000 with the noxious effect of an increased ultraviolet B/A ratio and the overproduction of heat shock proteins during the summer may be inferred to be the cause. Despite increased peak solar activity in 2000 the relapse count for the diseases was not greater in 2000 than 1998-1999. A mild inverse relationship was demonstrated for solar activity and the SpA relapse count during a three-year assessment period. We have seen that the timing of the relapse onset of inflammatory arthritis is almost independent of solar activity over a several year follow-up. But within one investigated year such a correlation may be seen and that may be either coincidental or reflective of a real relationship. This emphasizes the importance of following dynamic solar-relapse relationships for the inflammatory arthritides. The solar factor and other possible contributory factors should be further investigated.

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