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Seasonal variation in the onset of acute microcrystalline arthritis

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Abstract

Objective. To determine whether acute attacks of uric acid and calcium pyrophosphate microcrystalline arthritis show a seasonal variation and, if so, to verify whether the distribution of single episodes shows a rhythmic circannual pattern.

Method. All suspected cases of microcrystalline acute arthritis observed at the General Hospital of Ferrara during an 8 yr period (January 1990–December 1997) were considered. Diagnosis was made on the basis of history, physical examination and analysis of synovial fluid by means of polarized light microscopy. Month and day of each event were categorized both into four 3-month periods (by seasons) and 12 monthly intervals. Two different statistical methods have been utilized: χ^2 test for goodness of fit and partial Fourier series.

Results. During the period considered, 210 episodes of acute gout were observed [196 in males (93.3%) and 14 in females (6.7%)] in 179 different subjects, and 179 episodes of acute pseudogout [58 in males (32.4%) and 121 in females (67.6%)] in 165 different subjects. Gout attacks showed a higher frequency peak in spring [76 cases (36.2%), $P < 0.001$]. Analysis of distribution of events by gender confirmed the clear spring pattern in males (36.2%), whereas the paucity of cases in females did not allow any valid statistical analysis. Pseudogout attacks showed a higher frequency peak in autumn [52 cases (29.1%)], without reaching a statistically significant level either for the total sample or for subgroups divided by gender. Analysis of the seasonal distribution of gout or pseudogout events was significantly different (χ^2 15.7, $P = 0.001$). Chronobiological evaluation by means of Fourier analysis showed a circannual pattern for gout attacks, both for the total sample ($P = 0.006$) and the male subgroup ($P = 0.003$), characterized by a peak in April and a trough in October. Again, as for pseudogout events, no seasonal variation was found, either for the total sample or subgroups by gender.

Conclusions. The present study gives further confirmation that acute gout attacks exhibit a circannual distribution in their occurrence, being more frequent in April, whereas pseudogout attacks do not. Moreover, the seasonal distribution of gout and pseudogout acute events is significantly different.

KEY WORDS: Gout, Pseudogout, Circannual rhythm, Periodicity, Chronobiology.

Many studies have shown a temporal variation, e.g. circadian and/or circannual, in the onset of several acute diseases, especially related to cardio and cerebrovascular diseases [1, 2]. In the last few years, some studies dealing with chronobiological evaluation of rheumatic diseases appeared in the literature, offering interesting issues [3–5]. As for microcrystalline acute disease, the first reports suggesting a possible effect of weather conditions on gout go back to 1920.

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Williamson [6], in fact, found that gout attacks in Chicago were more frequent in spring (40% of events). Several years later, in Australia, McLeod [7] found a significant number of patients with gout in autumn, suggesting that the onset of cold weather could be a precipitating factor for recurrence of gout attacks. More recently, Arber *et al.* [8], in Israel, reported a higher frequency of gout attacks in spring and summer, with a significant peak in July. Only a few months ago, Schlesinger *et al.* [9] found that in Philadelphia acute gout (but not pseudogout) attacks are significantly more common in spring.

The aim of the present study was to determine, by means of a validated chronobiological analysis, whether

acute attacks of monosodium urate and calcium pyrophosphate microcrystalline arthritis show a rhythmic seasonal variation in a population of north-eastern Italy.

Subjects and methods

All cases of suspected microcrystalline acute arthritis observed in the emergency room and departments of internal medicine and rheumatology of St Anna Hospital, Ferrara, during an 8 yr period, from 1 January 1990 through December 1997, were considered. Ferrara is a town in Northern Italy with $\sim$150 000 inhabitants with a distribution of age, sex and socio-economic status similar to that of Italy as a whole. The population is almost exclusively white. The only available hospital in this community is St Anna Hospital, which also serves as the sole teaching centre for the school of medicine.

Diagnosis was made on the basis of history, physical examination and analysis of synovial fluid by means of polarized light microscopy. Patients with acute gout attacks were considered when synovial fluid had intracellular monosodium urate crystals and leucocyte counts $>$2000/mm3 or $>$10 leucocytes per high power field. Moreover, patients with acute pseudogout were considered when synovial fluid had intracellular calcium pyrophosphate crystals and leucocyte counts $>$2000/mm3 or $>$10 leucocytes per high power field [10].

The day and month of each event were categorized both into four 3-month periods (according with seasons) and into 12 1-month intervals.

Two different statistical methods have been utilized: x2 test for goodness of fit and partial Fourier series. The x2 test for goodness of fit was applied to the total sample population and subgroups by gender, comparing observed *vs* expected events during the four intervals by season [11].

Analysis of the rhythmicity of the events occurring in the single months of the year was performed by applying partial Fourier series with up to four harmonics (12, 6, 4 and 3 months) to the time series, using Chronolab software written for the Apple Macintosh computer [12]. The program permits, among all the possible combinations of the periods chosen by the user, the selection of the harmonic or the combination of harmonics that best explains the variance of data. The percentage of rhythms (PR) (percentage of overall variability of data about the arithmetic mean attributable to the fitted rhythmic function) and the probability value resulting from the *F* statistic used to test the hypothesis of zero amplitude were chosen to be reported in the results as representative parameters of goodness of fit and statistical significance of each fitted function, respectively. The program calculates the midline estimating statistic of rhythm (MESOR; the rhythm-adjusted mean over the time period analysed) and the amplitude (half the distance between the absolute maximum and minimum of the function) of the best-fitting curve. The program also calculates peak (orthophase) and trough (bathyphase) times of the fitted curve (times of occurrence of the absolute maximum and minimum) and the acrophase of each single harmonic (peak time of rhythmic change). Significance levels were always assumed for $P < 0.05$.

Statistical analysis was performed only considering the sample by gender. Conventional statistical analysis was performed using Student's test for unpaired data. Significance levels were always set at $P < 0.05$.

Results

From January 1990 to December 1997, 210 acute gout events were observed [196 in males (93.3%) and 14 in women (6.7%)] in 179 different subjects [mean age 57 $\pm$ 13 yr, 165 males (92.1%), mean age 56 $\pm$ 13 yr, and 14 females (7.9%), mean age 68 $\pm$ 10 yr, difference between sexes $t = -3.4$, $P < 0.001$] and 179 acute pseudogout events [58 in males (32.4%) and 121 in females (67.6%)] in 165 different subjects [mean age 70 $\pm$ 10 yr, 54 males (32.7%), mean age 67 $\pm$ 10 yr, and 111 females (67.3%), mean age 72 $\pm$ 10 yr, differences between sexes $t = -3.09$, $P = 0.002$]. The mean age of subjects suffering from acute pseudogout attacks was significantly higher than that of subjects presenting gout ($t = 10.9$, $P < 0.001$). Almost all the subjects (97%) were stable residents.

Table 1 shows the monthly distribution of both gout and pseudogout attacks, also by gender.

Gout attacks showed a higher frequency peak in spring [76 cases (36.2%), $P < 0.001$]. Analysis of the distribution of events by gender confirmed such a pattern only for males (35.2%), whereas the extreme paucity of females did not allow any valid statistical analysis. Pseudogout events showed their higher frequency peak in autumn [52 cases (29.1%)]. However, a significant level was not reached. Similarly, no statistically significant difference in the distribution of events was found after analysis by gender (Table 2).

Analysis of the distribution of events by season between gout and pseudogout attacks was found to be significantly different (x2 15.7, $P = 0.001$).

Chronobiological evaluation by means of Fourier analysis showed a clear circannual pattern for gout attacks, both for the total sample ($P = 0.006$, PR 63.8, MESOR 17.59 $\pm$ 1.04, amplitude 6.40 $\pm$ 1.52, acrophase $-98.4 \pm 12.8^\circ$) and male subgroup ($P = 0.003$, PR 67.8, MESOR 16.47 $\pm$ 0.92, amplitude 6.16 $\pm$ 1.34, acrophase $-93.5 \pm 11.7^\circ$), characterized by a single harmonic having its peak in April and trough in October; no significant seasonal variation was found in females ($P = 0.231$, PR 25.4, MESOR 1.12 $\pm$ 0.23, amplitude 0.58 $\pm$ 0.31, acrophase $-162.1 \pm 32.8^\circ$). Again, pseudogout events did not show a significant seasonal variation, either for the total sample ($P = 0.609$, PR 9.4, MESOR 14.64 $\pm$ 1.32, amplitude 1.91 $\pm$ 1.88, acrophase $-231.8 \pm 55.3^\circ$) or subgroups by gender (men, $P = 0.598$, PR 9.8, MESOR 4.77 $\pm$ 0.70, amplitude 0.70 $\pm$ 0.99, acrophase $-3.1 \pm 58.9^\circ$; women, $P =$ 0.114, PR 35.2, MESOR 9.87 $\pm$ 0.82, amplitude 2.68 $\pm$ 1.15, acrophase $-215.6 \pm 25.2^\circ$).

TABLE 1. Distribution of gout and pseudogout events, and subgroups by gender

Time	Gout			Pseudogout		
	Men ($n = 196$)	Women ($n = 14$)	Total ($n = 210$)	Men ($n = 58$)	Women ($n = 121$)	Total ($n = 179$)
January	18	–	18	5	5	10
February	19	2	21	10	10	20
March	17	1	18	4	10	14
April	24	1	25	5	5	10
May	26	2	28	2	8	10
June	21	2	23	5	13	18
July	12	–	12	5	13	18
August	14	2	16	4	13	17
September	13	2	15	1	9	10
October	10	1	11	9	14	23
November	14	1	15	4	8	12
December	8	–	8	4	13	17

TABLE 2. Seasonal distribution of gout and pseudogout attacks

	Number of patients	Winter *n* (%)	Spring *n* (%)	Summer *n* (%)	Autumn *n* (%)	Goodness of fit	
						x2	*P*
Gout							
Total	210	57 (27.1)	76 (36.2)	43 (20.4)	34 (16.2)	19.1	<0.001
Males	196	54 (27.6)	71 (36.2)	39 (19.9)	32 (16.3)	18.3	<0.001
Females	14	3 (21.4)	5 (35.7)	4 (28.6)	2 (14.3)	1.4	0.699
Pseudogouta							
Total	179	44 (24.6)	8 (21.2)	45 (25.1)	52 (29.1)	2.2	0.531
Males	58	19 (32.8)	12 (20.7)	10 (17.2)	17 (29.3)	3.6	0.302
Females	121	25 (20.7)	26 (21.5)	35 (28.9)	35 (28.9)	3.0	0.392

aSeasonal distribution of gout *vs* pseudogout patients = x2 15.7, $P = 0.001$.

Discussion

The present study confirms that the occurrence of gout attacks exhibits a circannual distribution, characterized by a spring peak in April. Our results agree with those reported by Williamson [6], McLeod [7] and, more recently, by Schlesinger *et al.* [9], but differ from those by Arber [8], who found a summer peak in July. It has to be stressed that, to our knowledge, this study is the first in which a validated chronobiological computerized analysis has been performed, to search not only for a simple frequency peak, but also a reproducible rhythmic pattern. This is not a secondary point since data from Schlesinger *et al.* [9], when analysed by means of a chronobiological method, did not show any significant rhythmic pattern ($n = 359$, PR 13.4%, MESOR 30.36 ± 1.64, amplitude 2.94 ± 2.4, acrophase -67.5 ± 43.9, $P = 0.487$). Our study also documents that the seasonal distribution of gout and pseudogout attacks is significantly different.

According to Schlesinger *et al.* [9], we did not find any significant seasonal variation in pseudogout attacks. Such events seem to be more frequent in autumn, with some differences in sex distribution (summer–autumn in males, autumn–winter in females), but statistical significance was not satisfied.

It is somewhat difficult to explain such a peculiar seasonal distribution and rhythmicity of gout attacks; however some speculations about this topic may be put forward.

Saaibi *et al.* [13] demonstrated the existence of a circannual variation in serum uric acid levels, finding summer mean levels significantly higher than spring and winter levels, with their highest in July. We have no data regarding this particular aspect; however, the seasonal variations reported by Saaibi *et al.* do not match the pattern of distribution of acute gouty episodes observed in our population.

There are conflicting opinions about the effects of weather conditions on rheumatic diseases [14, 15]. When the effects of some atmospheric variables on the incidence of acute gout attacks were controlled for, no correlations emerged between the incidence of gout attacks and either mean monthly temperature or humidity. However, it should be noted that MSU (monosodium urate) crystals may also be found in asymptomatic joints, where they are frequently intracellular, producing only mild inflammation [16]. Thus, the formation of new crystals is probably not needed for triggering a new attack. Changes occurring in the organism, i.e. biochemical and/or hormonal, during spring time may alter this

asymptomatic equilibrium, favouring the precipitation of gouty attacks.

To date, we have no valid hypothesis to explain the observed different seasonal pattern of distribution of gout and pseudogout attacks. Different sensitivity may exist for both these conditions to environmental (diet, temperature, physical activity) or metabolic factors (serum uric acid levels, Ca:P ratio, hormonal and/or biochemical modifications) able to play some role in conditioning crystal formation or precipitation and in modulating their phlogistic potential through perturbation of the local synovial microenvironment. Different pathogenetic pathways leading to the clinical appearance of monosodium urate or calcium pyrophosphate acute synovitis must also be considered [17–21].

Further studies, aimed at confirming these results on larger populations in different geographical areas are needed.

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