Seasonal Variations in Onset of Wegener's Granulomatosis: Increased in Summer?

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ABSTRACT. ***Objective.*** Investigators have reported significant seasonal variations of onset of Wegener's granulomatosis (WG), but those data were not confirmed by others. We reexamined the hypothesis of a seasonal pattern of onset of WG.

Methods. We conducted telephone interviews with 59 patients with newly diagnosed WG fulfilling the American College of Rheumatology criteria. Patients were identified having been enrolled from 2001 to 2004 by French hospitals in 2 multicenter therapeutic trials. The interviews investigated precisely how and when their disease had appeared to establish an index date, defined as the year and month of the first symptom(s) attributable to WG. Once telephone interviews had been completed, index dates were also retrieved from medical records.

Results. Among the 59 patients interviewed, 14 (24%) were unable to specify an exact month of WG onset. Based on the remaining 45 "informative" patients, the month of onset distribution varied significantly ($p = 0.03$, exact goodness-of-fit chi-square test), notably with a higher onset rate in August ($p = 0.001$). Seasonal distributions also differed significantly ($p = 0.01$), with an increased rate of summer onset (June-August) ($p = 0.001$). Index dates extracted from medical files showed that onset was also more frequent in summer ($p = 0.01$).

Conclusion. Our results confirm the seasonality in onset of WG, but unlike previous reports indicating an increase in winter, instead suggest that this vasculitis preferentially appears in summer. These findings might support an allergic mechanism in the pathogenesis of WG. (First Release July 1 2006; J Rheumatol 2006;33:1615–22)

Key Indexing Terms:
WEGENER'S GRANULOMATOSIS EPIDEMIOLOGY SEASONAL VARIATION

Wegener's granulomatosis (WG) is a primary systemic vasculitis classically associating ear, nose and throat (ENT), pulmonary, and renal involvement. However, this typical combination is inconstant and WG frequently affects a variety of other organs and/or tissues, resulting in highly polymorphous disease presentations. Diagnosis of this rare disorder is supported by histological features of vascular inflammation, granulomatosis and/or pauciimmune glomerulonephritis and — for about 90% of cases — by positive antineutrophil cytoplasm antibody (ANCA) serology most characteristically giving a cytoplasmic immunofluorescence labeling pattern (C-ANCA) and recognizing proteinase 3 (PR3), assessed by ELISA[1].

The etiology of WG is unknown and it remains insufficiently understood to what extent environmental and genetic factors contribute to its development. Several studies showed onset of WG to vary by season, with the incidence peaking in winter[2-6]. That important observation tended to support an underlying infectious factor[2-6], but other investigations failed to observe any significant seasonal variation[7,8]. To some degree, interpretation of the significance of these reports has been hampered by the small number of studies focusing on this issue[3,7] and by part of these data having been derived from populations also including other primary systemic vasculitides[2].

We reexamined the hypothesis of a seasonal pattern of onset of WG.

MATERIALS AND METHODS

Patient selection. Patients with WG selected for this study were identified through their participation in 2 prospective multicenter therapeutic trials, WEGENT and IMPROVE, respectively organized by the French (FVSG) and the European (EUVAS) Vasculitis Study Groups[9,10]. These trials concerned individuals with newly diagnosed systemic[10] or generalized[9] WG and microscopic polyangiitis (MPA). Through the collaborative FVSG network, patients were recruited from primary, secondary, or tertiary care facilities throughout France (and also from other European countries for WEGENT), with inclusion periods encompassing May 1998–May 2003 for WEGENT and June 2003–December 2004 for IMPROVE. For both trials, eligibility for inclusion and subsequent data collection were verified by staff members of the FVSG coordinating center (Hospital Cochin, Paris), with which the authors (AM, AA, CP, and LG) are affiliated.

All consecutive WG patients that had been enrolled by French hospitals in one of these 2 trials during the 4-year period from January 2001 to December 2004 were considered for this investigation. This timeframe was chosen to identify at least 50 patients, while attempting to ensure that patients

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might still be able to remember the precise mode and time that their disease had started. Owing to the slightly varying WG inclusion criteria used in the WEGENT and IMPROVE trials, we decided to retain for this study only those cases ultimately meeting the American College of Rheumatology (ACR) classification criteria[11].

During the selected period, the WEGENT and IMPROVE trials had recruited 71 and 27 patients with diagnoses of WG or MPA, respectively. Among the 71 WG patients (Figure 1), 3 had died at the time this investigation was planned (January 2005). After obtaining consent from the local treating physicians, we posted letters, explaining the purpose of the study and seeking written consent for their participation, to the 68 surviving candidates. Four patients refused to participate or did not reply, and 5 others failed to satisfy ACR classification criteria for WG[11], probably because their clinical diagnoses corresponded to MPA (3 patients) or to upper or lower respiratory tract-restricted WG (1 patient each) associated with extrarespiratory involvement but no histologically proven granuloma. Here, we refer only to the 59 WG patients ultimately analyzed.

Data collection. With those 59 patients, we conducted specific telephone interviews to obtain their medical history prior to WG diagnosis. To prepare patients for the inquiry, we enclosed with the initial letter requesting participation a questionnaire to elicit when the first signs of their disease appeared and what they were, by including a non-exhaustive list of 29 general or organ-specific symptoms that might be observed during this vasculitis. Patients were blinded to the previously formulated hypothesis of WG onset more frequently occurring in winter. Prior to launching the study, 2 of us (AM, NA) interviewed together 4 additional volunteers with WG to verify the comprehensibility of the questionnaire and to achieve consensus concerning the strategy of patient questioning.

All telephone calls were conducted during a 2-week period (late February/early March 2005) at the appointment times established by the patients themselves when they replied to the initial letter and returned the signed consent forms. Each telephone inquiry was conducted by the same investigator (NA) and required 20–60 minutes to complete. During the interview, each patient was asked to explain in detail the symptoms that had preceded WG diagnosis, their chronological sequence of occurrence, and the way they had responded to the trial regimen. We also sought potential prior episodes of WG-related disease, in particular ENT symptoms, which might not have been mentioned spontaneously by patients. Each reported symptom was recorded with its year, month, and, when applicable, week and day of occurrence. Further, we asked patients how they would describe the onset of their disease: acute (within days), rapidly progressive (within weeks), or insidious (within months).

To avoid bias, patients' medical files, including trial data record sheets and/or hospital discharge summaries and histology reports, were reviewed only after the telephone interviews had been completed to extract WG characteristics at diagnosis. Data on ANCA serologies were examined with regard to indirect immunofluorescence (IIF) and ELISA, and histological findings for vasculitis, extravascular granulomatosis, and/or pauciimmune glomerulonephritis. An organ system was considered to be involved based on histological proof and/or characteristic clinical features or, for pulmonary and central nervous system disease, documentation by imaging techniques. Renal disease was defined as kidney biopsy findings of pauciimmune glomerulonephritis and/or the presence of hematuria and/or proteinuria. From those documents, we also recorded the dates of trial inclusion and, as a surrogate for the time of diagnosis, the date the trial regimen had been initiated. We also searched the medical records for the date the first symptoms had appeared to compare them with those obtained during the telephone interviews. Data on disease onset from medical files were only recorded when a precise month had been given or could be calculated.

Once patients' interviews and data retrieval had been completed, we determined each patient's index symptom and date of WG onset. The index symptom was considered the very first WG manifestation, provided that it was compatible with the particular WG presentation at diagnosis, had persisted (continuously or intermittently) until diagnosis, and had, at least partially, responded to specific therapy. General manifestations, defined as fever, malaise, and/or weight loss, were also considered potential index symptoms. Index dates were assigned as at least month and year. The disease onset–diagnosis interval was calculated as the difference between onset of symptoms

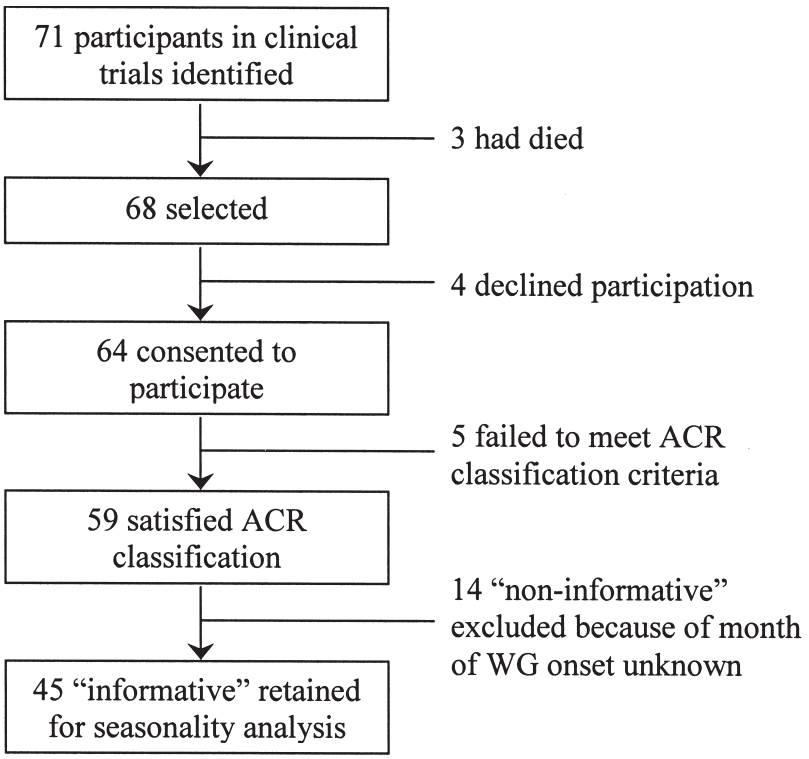

Figure 1. The WG study population.

and initiation of the trial regimen. For these calculations, index dates were arbitrarily set on the 15th day of the respective months, unless patients were able to specify further the week or day of disease onset. A similar procedure was applied for index dates retrieved from the medical files to enable calculation of the time interval separating the index dates obtained from the files and those obtained during the telephone interviews.

Statistical analysis. The distribution of symptom onset according to month or season was examined for uniformity using exact one-way goodness-of-fit chi-square tests[12] (StatExact, Cytel Software, Cambridge, MA, USA) as a means of identifying significant deviations from expected frequencies. According to meteorological definitions in the northern hemisphere, seasons were divided into spring (March–May), summer (June–August), autumn (September–November), and winter (December–February). Comparisons of seasonal distribution patterns for patient subgroups (sex, renal vs non-renal WG, acute vs rapidly progressive/insidious onset, calendar year of onset) were performed using Fisher's exact tests. Nonparametric Kruskal–Wallis tests were used to compare continuous variables. For all statistical analyses, a 2-tailed $p < 0.05$ was considered significant.

RESULTS

Characteristics of the study population. The main characteristics at diagnosis for the 59 WG patients are summarized in Table 1. They satisfied 2 (n = 32), 3 (n = 21), or 4 (n = 6) ACR criteria. Histological evidence of vasculitis, granulomatosis, and/or pauciimmune glomerulonephritis had been obtained for 47 (80%) patients. All but one of the 12 patients not having histologically-proven WG had positive C-ANCA/anti-PR3 serology; the remaining patient was C-ANCA-positive but ELISA was negative for anti-PR3 or myeloperoxidase.

Analysis of telephone interview data revealed that 14 (24%) of the 59 patients were unable to date WG onset precisely. Most frequently, these patients could at best assign start of their disease to a period lasting several months or were totally unable to recall the time of onset. In view of the specific aim of our study, these 14 individuals were considered "noninformative" and we consequently retained the data of 45 "informative" patients for the primary objective of this study (Figure 1). Comparison of WG characteristics between the 45 informative and the 14 noninformative patients showed that the latter had a significantly lower frequency of renal involvement ($p = 0.006$) and tended to have general symptoms less frequently ($p = 0.05$) (Table 1). For the 45 informative individuals, trial inclusions and initiations of specific therapy were equally distributed over the year (chi-square 13.40, 11 df, $p = 0.28$ and chi-square 8.60, 11 df, $p = 0.69$, respectively; Figures 2A and 2B) and the 4 seasons (chi-square 0.42, 3 df, $p = 0.95$ and chi-square 3.80, 3 df, $p = 0.31$). The respective distributions of these 2 variables over the year (chi-square 18.11, 11 df, $p = 0.08$ and chi-square 10.35, 11 df, $p = 0.52$) and seasons (chi-square 1.00, 3 df, $p = 0.82$ and chi-square 3.03, 3 df, $p = 0.40$) also did not differ significantly for all 59 patients we interviewed.

Index symptoms. Table 2 summarizes the first clinical manifestation(s) and self-reported mode of onset as described by the 45 informative patients. ENT signs were the most frequently reported first symptoms (42%) and appeared to be the only initial manifestation for 29% of these patients. ENT manifestations included nasal and sinus complaints (nasal obstruction, discharge, crusting, or bleeding; tenderness/pain over paranasal sinuses) in 79% and/or ear signs (hearing loss, internal tenderness) in 32%. Respiratory signs (16%) always included a cough (100%). Fatigue was reported as the first manifestation by 13% and represented the only initial com-

Table 1. Principal patient characteristics at diagnosis for all 59 WG patients fulfilling selection criteria, and as a function of ability ("informative") or not ("noninformative") to specify the month of disease onset.

Variable	Patients		
	All	Informative	Noninformative
Patients, n	59	45	14
Demographics			
Mean age, yrs (± SD)	54.3 ± 13.7	53.5 ± 14.4	56.9 ± 11.2
Sex (M/F)	37/22	30/15	7/7
Disease presentation, %			
General symptoms*	97	100†	86†
ENT involvement	93	91	100
Pulmonary involvement	63	62	64
Glomerulonephritis	69	80††	36††
Ophthalmological involvement	32	31	36
Peripheral neuropathy	32	31	36
Cutaneous involvement	24	20	36
ANCA positivity, %	95	98	86
C-ANCA — specificity unknown	2	0	7
C-ANCA/anti-PR3	83	87	71
C-ANCA/anti-MPO	2	2	0
P-ANCA/anti-MPO	8	9	7
Histological proof, %	80	80	79

WG: Wegener's granulomatosis. MPO: myeloperoxidase. * General symptoms were defined as fever, malaise and/or weight loss. † $p = 0.05$; †† $p = 0.01$.

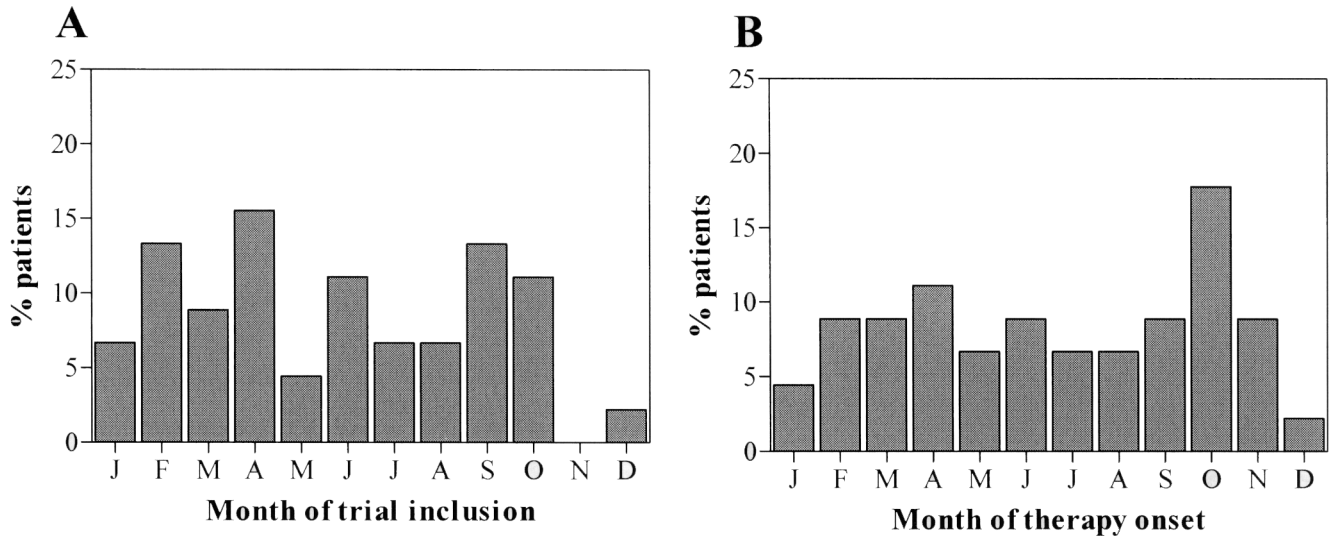

Figure 2. Distributions of trial inclusion (A) and therapy onset (B) by month for the 45 "informative" patients. A: chi-square 13.40, df 11, p = 0.28. B: chi-square 8.60, df 11, p = 0.69.

Table 2. Self-reported initial symptoms and mode of WG onset based on 45 "informative" patients.

Variable	%
First symptom(s)*	
ENT	42
Respiratory	16
Arthralgias/arthritis	16
Unusual fatigue	13
Neurological	11
Myalgias	9
Fever	7
Cutaneous	2
Ophthalmological	2
Weight loss	0
Others†	13
Mode of disease onset	
Acute (within days)	42
Rapidly progressive (within weeks)	40
Insidious (within months)	18

* Summing of percentages exceeds 100% because patients could indicate multiple symptoms. † Including: dental/gingival pain (7%), rib pain, leg edema, foot pain (2% each).

plaint for 9%. Conversely, the patients who reported fever as the starting symptom (7%) also had associated organ-specific symptoms. Weight loss was not mentioned by any of the patients as the initial sign. Surprisingly, 9% of patients complained of dental or gingival pain as the first symptom, which was associated with ENT/pulmonary symptoms or arthralgias in all of them. The mean overall onset–diagnosis interval was 7.7 ± 7.4 months (range 0.8–32.6).

Monthly and seasonal variations of WG onset. Monthly and seasonal distributions of WG onset as reported during the telephone interviews of the 45 informative patients are shown in Figures 3A and 3B. Frequency of disease onset according to month showed a significant variation (chi-square 21.93, 11 df, p = 0.03) with a notable peak in August (24% of the patients). August onset was significantly higher than the rest of the year (chi-square 15.29, 1 df, p = 0.001). Similarly, the seasonal distribution of symptom onset differed significantly (chi-square 11.44, 3 df, p = 0.01), with a higher onset rate in summer than the 3 other seasons combined (chi-square 11.23, 1 df, p = 0.001). Analyses of the seasonal patterns by stratification for selected variables found no significant differences (Table 3).

Information on the index dates was gathered from the medical files of 53 of the 59 patients fulfilling the selection criteria. Comparisons showed that index dates provided during the 45 informative patients' telephone interviews predated those extracted from their medical files by a mean of 2.6 ± 6.6 months (median 0.5 mo; range –11.9 to 29.0; 2 missing values). Figure 4 illustrates the individual intervals between the 2 dates according to the month of WG onset as related during the telephone interviews. Using this data set collected from the medical files, analyses still showed higher onset rates in summer for both the 45 informative patients (44%) (chi-square 7.76, 1 df, p = 0.01; 2 missing values) and the 53 individuals for whom this information was available (42%) (chi-square 0.60, 1 df, p = 0.01). The monthly distribution of disease onset differed slightly, with the highest rate in July for the 45 informative patients (23%) (chi-square 11.94, 1 df, p = 0.003; 2 missing values) and the 53 assessable subjects (23%) (chi-square 13.10, 1 df, p = 0.001).

DISCUSSION

Our study was designed to test the hypothesis of seasonality in the onset of WG, particularly in light of previously reported observations that this disease starts more frequently in winter[2-6]. Intriguingly, we found a statistically significant peak onset in summer, and especially in August. Seasonal fluctuations in WG onset pointed to the same patterns in both the

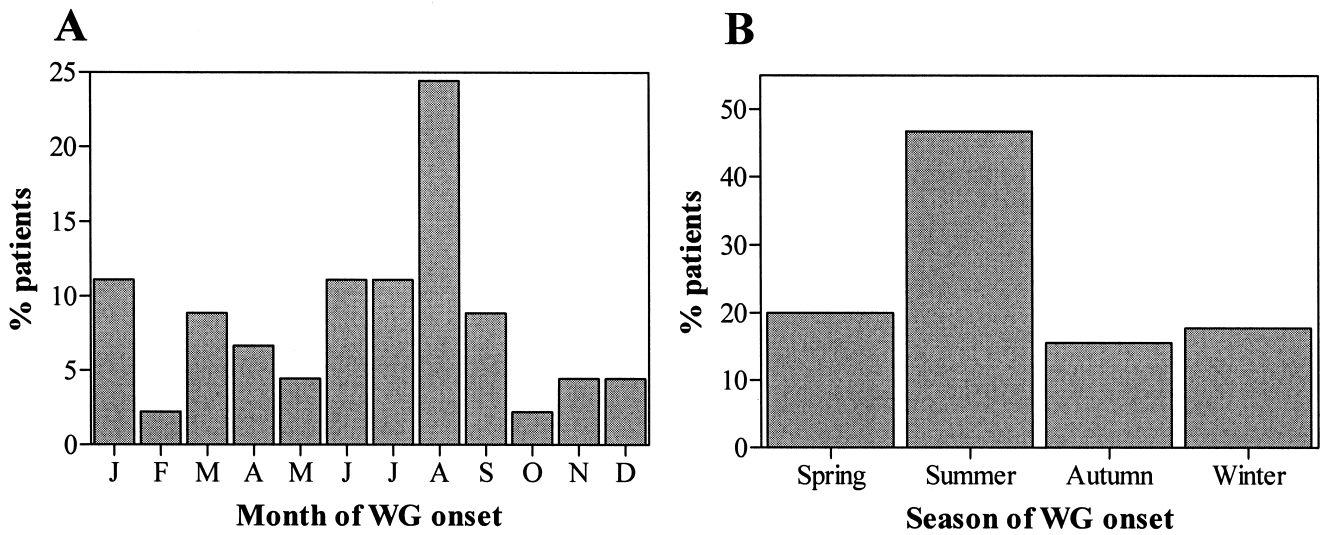

Figure 3. Distributions of month (A) and season (B) of WG onset for the 45 "informative" patients as related in telephone interviews. A: chi-square 21.93, df 11, p = 0.03. B: chi-square 11.44, df 3, p = 0.01.

Table 3. Seasonal variations (%) of WG onset stratified for selected variables (p refer to comparisons of distributions across strata).

Variable	Patients, n	Season of Onset, %				p
		Spring	Summer	Autumn	Winter	
Sex						0.29
Male	30	23	43	10	23	
Female	15	13	53	27	7	
Renal involvement						0.16
Yes	36	25	44	11	19	
No	9	0	56	33	11	
Self-reported mode of WG onset						0.62
Acute	19	11	53	16	21	
Rapidly progressive/insidious	26	27	42	15	15	
Calendar year of WG onset						0.66
≤ 2000	12	17	42	33	8	
2001	11	18	36	18	27	
2002	10	20	60	10	10	
≥ 2003	12	25	50	0	25	

sexes, renal and non-renal WG, several calendar-year periods, and self-reported mode of disease onset.

Investigating seasonal variations of onset of diseases is a widely used epidemiological approach to provide indirect information into their pathogeneses. Indeed, recognizing seasonal clustering in the onset of a given illness strongly supports an influence of risk or causal factors with known circannual variations. In this setting, seasonality is readily attributed to climate-related environmental factors[13,14], but they may also be explained by endogenous chronobiological changes over the year in hormone concentrations[15] or immune functions[13,14,16]. Extrapolation of seasonality findings to a specific causal or triggering factor therefore requires consideration of the time of predominant occurrence but also hypotheses on potentially underlying pathophysiological mechanisms.

Our results are at variance with all previously published observations on seasonality of WG onset (Table 4). However, similar heterogeneous findings were obtained for another vasculitis, giant-cell arteritis, with onset reportedly predominantly occurring in winter[17,18], summer[18-21], or with no seasonal pattern[3]. Such inconsistencies perhaps reflect true differences among geographically remote areas, but they may also be a likely consequence of the difficulty of accurately determining the moment that a chronic disease first becomes apparent. Indeed, although the WG diagnoses were made not more than 4 years ago, 24% of the patients we interviewed were unable to specify the month their disease had started, a finding similar to that noted in an analogous study on polymyalgia rheumatica[22]. In the remaining patients, the dates of WG onset collected from medical files perceptibly diverged — by an average of 2.6 months — from those obtained during their telephone interviews. Although patient- and physician-based

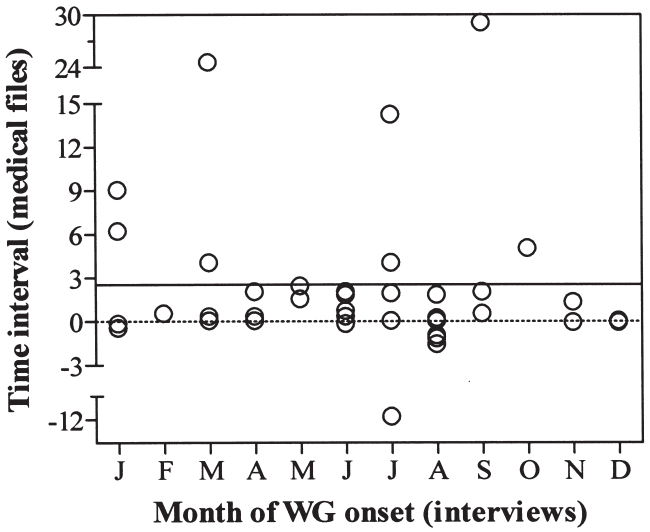

Figure 4. Time interval (months) separating the dates of WG onset retrieved from medical files compared to those determined during specific telephone interviews (shown for 43 patients for whom both dates were obtained and according to the calendar month of onset of WG). Solid line indicates mean 2.6 months.

data sets yielded comparable general findings on seasonality, our observations may raise the question of the reliability of those studies' results primarily based on information routinely reported in medical files[2-6,8], because that approach apparently shifted the overall time of disease onset to a slightly later period.

The investigators who found that WG onset clustered in winter mainly emphasized that their finding reflected the link between WG and infection[2-6]. Because of the frequently prominent airway disease, respiratory infection has indeed long been suspected as a possible precipitating or etiological factor of WG[23,24]. However, further acceptance of this theory remains hampered because no specific microorganism has yet been associated with WG onset and the most compelling negative data stemmed from the analysis of bronchoalveolar lavage fluids using microbiological and molecular biology techniques[25]. Nevertheless, this notion of an infectious agent playing an important part is still conceivable with respect to our findings of more frequent WG onsets in summer. Despite the rather low overall incidence of infection during this season, those attributed to rhinovirus peak from spring through autumn, causing mild respiratory illnesses[26] that would be consistent with the first signs experienced by many patients with WG.

The results of our study also help put other pathogenic hypotheses into perspective. One could suppose that the high summer rate of WG onset might be explained by exposure to sunlight or air pollutants, but this assumption appears difficult to reconcile with observations of increasing WG frequency with latitude[27] and equal prevalences in rural and urban regions[28]. The hypothesis that is most appealing to us is that our findings point towards a role of allergy. Spring and summer are indeed characterized by prominent release of pollens[29], a major cause of allergic rhinitis and asthma[30], that induce clinical pictures closely resembling those of many patients at WG onset. Pertinently, case–control studies suggested that WG was associated with a history of allergy[31-33], and both WG[27] and allergy[34-36] probably share epidemiological features with higher frequencies in northern Europe and rising incidences over the last few decades[8,34,36]. Although still controversial[37], it has furthermore been demonstrated that WG-related nasal disease might result from an "allergy-like" Th2-driven immune response[38]. Thus, despite our and previously reported findings on Kawasaki disease[39] that might highlight pollen allergy as a promoter of vasculitides, pollen should probably not be considered the sole allergen responsible in this setting.

Because the patients we investigated were identified through their participation in prospective multicenter trials, a theoretical weakness of our study could be that it reflected varying seasonal propensities to include patients. However, patient enrollment in these trials and therapy initiation appeared to be fairly uniform over the calendar year, and we think that this potentially confounding effect should have been further tempered by the widely variable interval between onset of disease symptoms and diagnosis. Even so, we recognize that the non-population–based design of our investigation limits the possibilities of more in-depth deciphering of the

Table 4. Seasonal distribution of WG onset in our and previous studies.

Authors	No. of Patients	Study Area	Data Source	Season of Onset, %			
				Spring	Summer	Autumn	Winter
Falk[2]	70*	US	Medical records	28	11	23	38
Raynauld[3]	84	North America	Medical records	35	14	21	30
Carruthers[4]	21	UK	Medical records	24	33	0	43
Blockmans[5]	50	Belgium	Medical records	38 (April–Sept.)		62 (Oct.–March)	
Tidman[6]	19	Sweden	Medical records	37	11	16	37
Duna[7]	101	US	Specific interviews	19	22	31	22
Koldingsnes[8]	55	Norway	Medical records	29	24	24	24
Our study	45	France	Specific interviews	20	47	16	18

* Including 37 patients with WG and 33 patients with microscopic polyangiitis.

causes for our findings. Another limitation to bear in mind is that the evaluated individuals were relatively few in number and, because they differed to some extent from the noninformative patients excluded, might not be fully representative of WG in general.

At present, WG should be viewed as a multifactorial disease resulting from the interplay of environmental triggers in genetically predisposed individuals. The most convincing evidence for the input of genetics comes from identification of a number of candidate susceptibility genes[40] and findings suggesting that WG preferentially affects subjects of Caucasian ethnicity[41]. In contrast, other studies found associations of WG with silica or silica-containing compounds[32,42,43], farming, or exposure to solvents[32] or industrial pollutants[33]. Our and former observations[2-6] of the seasonal variations of WG onset would not only strengthen the environmental as opposed to the genetic theory, but also indicate that at least some of the triggering or causal factors would act (sub)acutely rather than by means of cumulative exposure. Further evidence in favor of this concept is provided by observations of periodic fluctuations in WG incidence[8].

Our findings add support to WG onset exhibiting seasonal variations, as they indicate for the first time that WG might start more frequently during summer months. These results lend plausibility to the importance of environmental factors acting in the short term and, although the influence of infection is not ruled out, they might raise speculation about a triggering or etiological role of atopy. In light of the divergent observations reported so far and their potential contribution to the understanding of WG pathogenesis, seasonality of onset may still warrant further careful examination.

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