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Temporal Case Clustering in Pityriasis Rosea

A Regression Analysis on 1379 Patients in Minnesota, Kuwait, and Diyarbakir, Turkey

Antonio A. T. Chuh, MD(HK), MRCP(UK), FRCP(Ire), MRCPCH; Nicolas Molinari, PhD; Gabriel Sciallis, MD; Mehmet Harman, MD; Sedat Akdeniz, MD; Arti Nanda, MD, DNBE

Objective: To detect temporal case clustering in patients with pityriasis rosea in different geographic locations.

Design: Regression analysis of dates on which 1379 patients were diagnosed as having pityriasis rosea in 3 different geographic locations. The control data consisted of dates of diagnosis of patients with psoriasis in the same settings.

Setting: Dermatology clinics in Kuwait, Minnesota, and Diyarbakir, Turkey.

Patients: Patients with pityriasis rosea and psoriasis seeking care in the clinics.

Results: Three significant positive clusters ($P=.005$, $P=.001$, and $P=.01$, respectively) and 1 significant negative cluster ($P<.001$) were detected in these series of patients. No cluster was detected in 2 corresponding series of patients with psoriasis in Kuwait and Turkey.

Conclusion: Temporal case clustering exists in pityriasis rosea.

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Author Affiliations: Department of Medicine, University of Hong Kong and Queen Mary Hospital, Pokfulam, Hong Kong (Dr Chuh); Department of Biostatistics, Institut Universitaire de Recherche Clinique, University of Montpellier I, Montpellier, France (Dr Molinari); Department of Dermatology, Mayo Medical School, Mayo Clinic, Rochester, Minn (Dr Sciallis); Department of Dermatology and Venereology, University of Dicle, Diyarbakir, Turkey (Drs Harman and Akdeniz); and Department of Pediatric Dermatology, Asad Al-Hamad Dermatology Center, Al-Sabah Hospital, Kuwait (Dr Nanda).

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THE CAUSE OF PITYRIASIS rosea (PR) is unknown. Studies on the association of PR with human herpesvirus 7 infection[1-10] have yielded conflicting results. Recent studies have reported no evidence of PR associated with cytomegalovirus, Epstein-Barr virus, parvovirus B19,[11] *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *Legionella long-beachae*, *Legionella micdadei*, *Legionella pneumophila*, and *Mycoplasma pneumoniae*[12] infections.

Determining whether the epidemiological evidence supports an infectious origin is important, because it supports the need for a further laborious search for the pathogen. Cluster analysis is one such approach and has been applied in such diseases as childhood leukemia[13] and Kawasaki disease.[14] In 1982, Messenger et al[15] reported significant spatial-temporal clustering among female patients with PR in primary care settings, but not among male patients. They also reported a temporal cluster of 16 cases within a 28-day period.

Two of us (A.A.T.C. and N.M) previously reported the findings of a multicenter retrospective study in patients with PR in Hong Kong.[16] Atopic dermatitis and scabies were analyzed concomitantly as control conditions, the former as a negative control (noninfectious, temporal clustering not expected to be detectable) and the latter as a positive control (infectious, temporal clustering expected to be detectable). We detected 3 statistically significant clusters ($P=.03$) among our patients with PR, no significant cluster among our patients with atopic dermatitis, and 1 significant cluster ($P=.025$) among our patients with scabies.

If our hypothesis is true, it would be expected that temporal clusters would also be detectable among patients with PR in other time frames and geographic locations. We performed a systematic analysis of 3 previously reported series involving a total of

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1379 patients with PR in 3 separate locations. Our aim was to detect temporal case clustering in these series of patients. Two corresponding series consisting of a total of 366 patients with psoriasis were also analyzed as controls. Psoriasis was selected as a control condition because it is not an infectious condition, and, to the best of our knowledge, there have been no reports of temporal case clustering of psoriasis.

METHODS

One of us (N.M.) developed a method based on a regression model to detect multiple temporal clusters.[17] This method does not impose to divide the period. It detects time windows with excess events and is effective with multiple clusters. For any position of the window, the entire period of observation is scanned continuously. Positive as well as negative (periods with significantly fewer events) clusters can be detected. The existence of 1 or more clusters is determined by bootstrapped simulations that allow the robustness of the test to be increased. The validity of this method has been established by applying it to the classic Knox data set[18] and to 62 spontaneous hemoptysis admissions at Nice Hospital in France.[19]

Once the cluster bounds were computed for each model, the model with the smallest Akaike information criteria[20] value was selected to determine the number of clusters. This means that we selected the model with the smallest expected loss of information, or the best approximation to the "true" model. To avoid sample effects and to obtain a *P* value, the criteria were computed again on 1000 bootstrapped samples. The *P* value corresponded to the percentage of bootstrapped samples for which the cluster model was selected with the Akaike information criteria against the nonclustering model.

One of us (A.A.T.C.) searched MEDLINE using the keywords *pityriasis rosea* and retrieved reports of all epidemiological studies on PR published between January 1, 1972, and December 31, 2001 (30 years). Then, letters were sent by post to the first authors of these studies or to the dermatology departments where these studies were conducted if the addresses of the first authors were not available. All authors were asked to retrieve the dates on which the diagnoses of PR were made for the series of patients reported. Also, the authors were asked to provide the dates on which a series of patients were first diagnosed as having psoriasis in the same setting within the same period to serve as controls. Approvals from review boards were sought where local regulations apply.

One of us (N.M.) then analyzed the extent of temporal clustering in each series of patients by a method based on a regression model.[17] Each data set was first transformed to produce values corresponding to the time between successive cases. These values were estimated using a constant under the nonclustering, or random, hypothesis. On the contrary, a piecewise constant model improves the fitting. This method was applied to obtain several models with different numbers of clusters for each series of patients.

RESULTS

Thirteen epidemiological studies[5,15,21-31] on PR were identified. One study [5] was a seroepidemiological study aimed at detecting human herpesvirus 6 and 7 infections by serologic analysis and by polymerase chain reaction analysis. Another[31] was a cross-sectional study based on 1-day surveys. Letters were sent to the first authors or the dermatology departments regarding the other 11 studies. Replies were received from the authors of 4 studies.[23,24,28,29] Investigators in São Paulo, Brazil, were unable to send us the complete data from their study, the findings of which were reported in 1984.[24] Investigators in Kuwait,[29] Minnesota,[23] and Turkey[28] were able to contribute data.

Data on a total of 1379 patients with PR and 366 patients with psoriasis were available for analysis. One of us (A.N.) retrieved data on 154 patients (all children younger than 12 years) with PR in Kuwait from 1992 to 1998 and on 197 patients (all children younger than 12 years) whose psoriasis was diagnosed in the same setting from 1993 to 1994 for the control data. Two of us (M.H. and S.A.) retrieved data on 286 patients with PR in Diyarbakir, Turkey, from 1993 to 1995 and on 169 patients whose psoriasis was diagnosed in the same setting in 1995 for the control data. One of us (G.S.) sought approval from the internal review board and retrieved data on 939 patients with PR in Rochester, Minn, during a period of 10 years (1969-1978). Owing to the long lapse of time, a corresponding set of data on patients whose psoriasis was diagnosed in the same period was not available for analysis.

The patients and controls from Kuwait and Diyarbakir, Turkey, were seen by dermatologists. Most were referred patients. Of the 939 patients with PR from Minnesota, 57% were seen by dermatologists, while 43% were seen by internal medicine physicians or general practitioners. Most of the patients seen by dermatologists were referred, while a proportion of the patients seen by internal medicine physicians or general practitioners were not. For all series of patients, no active effort was made to recruit the patients to minimize referral bias.

The results of our analysis are summarized in the **Table**. In the series of patients with PR from Kuwait, 1 significant temporal cluster was detected. **Figure 1**A shows the cluster analysis results and the interval between successive cases. A short mean time between successive events indicates a cluster. The single-cluster statistical model has a significant value ($P=.005$) compared with the nonclustering statistical model. The former model detects a cluster of 35 cases between September 19, 1994, and April 30, 1995. The significant cluster is seen as a depression in the center of the figure.

For the corresponding set of data on patients with psoriasis from Kuwait, no significant cluster was detected. The uniform distribution (nonclustering) regression model (Figure 1B) was selected by Akaike information criteria, ie, best approximation to the true model.

In the series of patients with PR from Minnesota, 2 significant clusters were identified. A cluster of 98 cases was detected from October 17, 1972, to May 24, 1973 ($P=.001$). Another cluster of 59 cases was detected from October 28, 1974, to April 16, 1975 ($P=.01$). The cluster analysis result is not shown because, with a total of 939 events, the figure is congested and has low readability.

In the series of patients with PR from Turkey, a significant negative cluster (period with significantly fewer events) of 152 days was detected between May 12, 1994, and October 10, 1994 ($P<.001$). A positive cluster of 15 cases was also detected between November 25, 1993, and December 3, 1993. However, this cluster is statistically insignificant ($P=.14$). **Figure 2**A shows the cluster analysis results for the series of patients from Turkey. The posi-

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Table. Cluster Analysis Results in 5 Series of Patients

Series of Patients With Dermatologic Conditions	Location	Dates	No. of Patients	Results of Cluster Analysis by a Regression Model
Pityriasis rosea	Rochester, Minn	January 1969 to December 1978	939	Two significant positive clusters of 98 cases ($P = .001$) and 59 cases ($P = .01$) were detected
Pityriasis rosea	Kuwait	January 1992 to December 1998	154 (age, <12 y)	One significant positive cluster of 35 cases ($P = .005$) was detected
Pityriasis rosea	Diyarbakir, Turkey	January 1993 to December 1995	286	One significant negative cluster of 152 days ($P < .001$) and 1 nonsignificant positive cluster of 15 cases ($P = .14$) were detected
Psoriasis	Kuwait	January 1993 to December 1994	197 (age, <12 y)	No significant positive or negative cluster was detected
Psoriasis	Diyarbakir, Turkey	January 1995 to December 1995	169	No significant positive or negative cluster was detected

tive cluster is seen as a depression, and the subsequent negative cluster is seen as an elevation.

For the corresponding set of data of patients with psoriasis from Turkey, no significant cluster was detected. The nonclustering regression model (Figure 2B) was selected as the best approximation to the true model.

COMMENT

There are many limitations in clustering methodology. The choice of an appropriate analysis method is difficult. The cell-occupancy approach[32] needs to divide the period into disjoint subintervals arbitrarily. For the scan test,[33] an arbitrary scanning window size has to be defined. To obviate the need for such a definition, a scan test with a variable window size[34] can be applied. However, this test only considers clusters with a fixed minimal number of events a priori, 5 for example. The rank-order procedure[35] is sensitive only to unimodal clustering and cannot distinguish between multiple clusters and randomness. Another limitation is that factors other than an infectious origin might lead to temporal clustering.

Presented as case reports, the phenomenon of temporal clustering in PR is not novel. Bosc[36] described 2 sisters with the successive onset of PR 61 days apart. Davis[37] described a 60-year-old farmer with PR whose 30-year-old daughter developed PR 3 months later. Halkier-Sorensen[38] described a 39-year-old woman whose PR recurred annually for 5 years. Her husband had a severe episode of PR 6 years earlier. There have been other reports of 2 or more cases of PR occurring in the same family or intimate environment.[39] However, these cases may be coincidental.

In 1982, Messenger et al[15] reported the first study on case clustering in PR. Their findings have been criticized because the degree of clustering that they found might not be sufficient to support an infectious hypothesis.[40] Control data were not analyzed concomitantly. Moreover, the rationale for their choosing a window size of 28 days was not stated. Clusters can be shorter or considerably longer than 28 days, and the cases in the aforementioned reports[36,37] were separated by 2 to 3 months. The prospective nature of their study might also have led to enthusiasm of par-

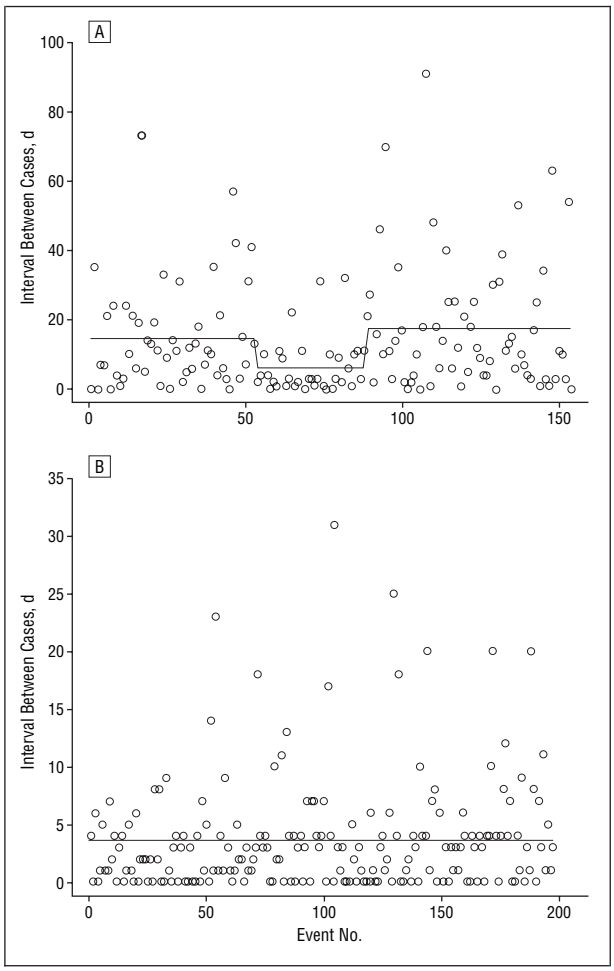

Figure 1. Cluster analysis results for patients with pityriasis rosea (A) and psoriasis (B) in Kuwait. A, Results in a series of 154 children with pityriasis rosea. This single-cluster model has a significant value ($P = .005$) compared with the nonclustering model. A cluster of 35 cases is seen as a depression in the center. B, Results in a series of 197 children with psoriasis. No significant cluster was detected. The uniform distribution regression model was selected using Akaike information criteria. No depression or elevation was noted.

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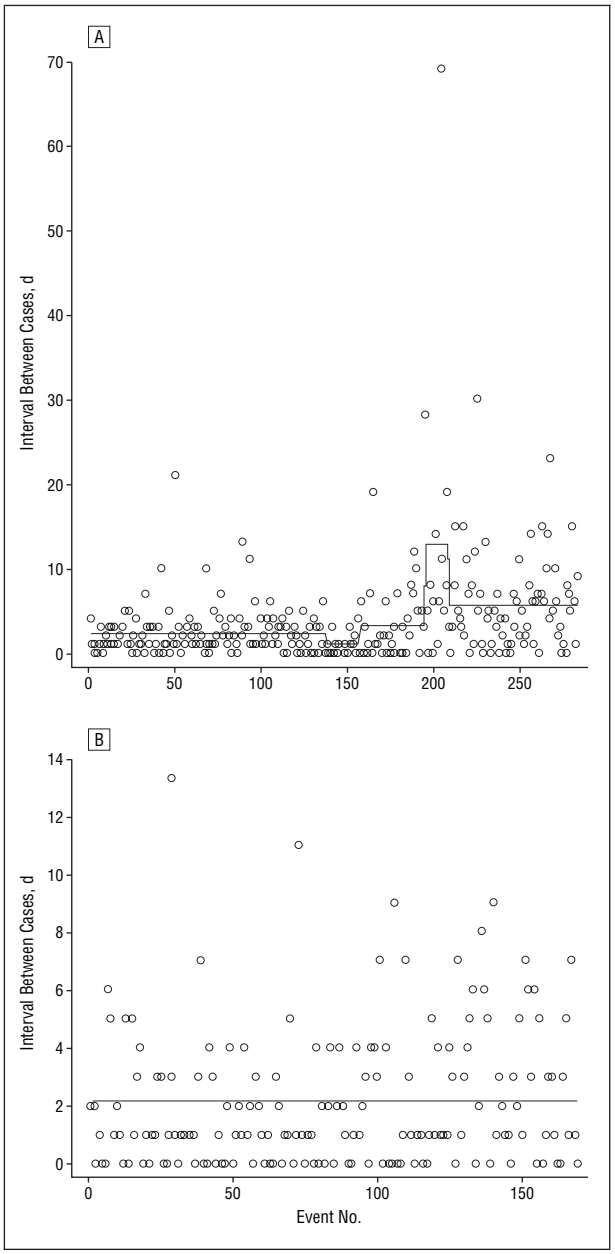

Figure 2. Cluster analysis results for patients with pityriasis rosea (A) and psoriasis (B) in Diyarbakir, Turkey. A, Results in a series of 286 patients with pityriasis rosea. An insignificant positive cluster of 15 cases ($P=.14$) is seen as a depression, and a subsequent significant negative cluster of 152 days ($P<.001$) is seen as an elevation. B, Results in a series of 169 children with psoriasis. The uniform distribution regression model was selected using Akaike information criteria. No depression or elevation was noted.

ticipating general practitioners in reporting the cluster.[15] Another prospective study in PR also found reporting bias.[31] In this regard, retrospective studies may paradoxically be superior because such reporting bias is absent.

Using a regression model and applying Akaike information criteria for selecting models, we undertook the first systematic attempt in proving that case clustering does occur in PR in different time frames and in separate geographic locations. We detected 3 statistically significant temporal clusters and 1 significant negative cluster in our 3 series of patients. In contrast to the study by Messenger et al,[15] we adopted a retrospective approach to eliminate reporting bias that has been found in prospective studies.[31] Our method was not based on an arbitrarily predetermined window size. Entire periods of observation were scanned continuously. We also analyzed corresponding series of patients whose psoriasis was diagnosed in the same settings and in the same time frames as controls. Our results should therefore provide adequate evidence to refute a random or nonclustering hypothesis for the occurrence of PR and establish the presence of temporal clustering in PR. We believe that such temporal clustering supports an infectious origin for PR and that further microbiological studies to search for the pathogen are indicated.

The underlying factors for the significant negative cluster found in the series of patients in Turkey in 1994 are obscure. Two of us (M.H. and S.A.) reviewed the climate and administrative conditions by means of qualitative interviews with the department staff and by qualitative review of the departmental records. We were unable to pinpoint any remarkable alteration in the climate of the region or in the organization or referral pattern in the dermatology department in 1994. We would have to assume that the negative cluster corresponded to a natural trough in the epidemiological pattern of this condition. It is well known that natural troughs do exist for many viral infections.[41]

Apart from the limitations mentioned in the introduction, another limitation of this study is that data from only 3 geographic locations were available for analysis. We failed to recruit more investigators into the project. Moreover, only psoriasis was used as a control condition. We also failed to retrieve data for other conditions as control data. Owing to the long lapse of time, a corresponding set of data on controls from Minnesota was not available for analysis.

A possible source of bias in our study is that most of our patients with PR were referred. We admit that a referral bias could be a confounding factor for the clustering phenomenon. However, as no active recruitment effort was made, referral bias should be minimal. Moreover, the durations of our clustering were more than 5 and 7 months for patients in Minnesota, more than 7 months for patients in Kuwait, and more than 4 months for the negative cluster of patients in Diyarbakir, Turkey. With such long durations of clusters, referral bias might have a small effect on our analysis results. Our 2 series of control patients were also referred, and no significant clustering was detected.

CONCLUSIONS

Using a regression model and applying Akaike information criteria for selecting models, we detected 3 statistically significant temporal clusters and 1 significant negative cluster in our 3 series of 1379 patients with PR from 3 separate geographic locations. No cluster was found in 2 series of 366 patients with psoriasis diagnosed in the same settings. We conclude that cases of PR do not occur at random. We believe that the presence of temporal case clustering supports an infective origin for PR and that further studies to search for the pathogen are indicated.

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Correspondence: Antonio A. T. Chuh, MD(HK), MRCP(UK), FRCP(Ire), MRCPCH, Bonham Surgery, Shop B5, Ning Yeung Terrace, 78 Bonham Rd, Ground Floor, Hong Kong (achuh@iohk.com).
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