

Some risk factors of rheumatoid arthritis: a case-control study

Dr. J.P.A. Puvimanasinghe¹, Dr. E.A. Padmasiri²,
Prof. L.C. Rajapaksa³.

Abstract

Objectives: To ascertain the association of three risk factors, namely stress, urinary tract infection and a family history of the disease, with the development of rheumatoid arthritis.

Methods: An unmatched case-control study was conducted in order to investigate some of the risk factors contributing to the development of rheumatoid arthritis in adult females. The study included 106 cases of rheumatoid arthritis and 212 controls comprising a wide spectrum of surgical and E.N.T. patients, and was conducted at two teaching hospitals in Colombo. Information on patient characteristics and preceding stress, focal infection and a family history of rheumatoid arthritis were collected with the aid of an interviewer-administered questionnaire.

Results: Univariate analysis revealed that age ($t=6.22$, $P<0.001$), stress ($OR=3.61$, 95% $CI:2.13-6.16$) and a family history of the disease ($OR=5.03$, 95% $CI:2.66-9.55$) were significant risk factors of rheumatoid arthritis. A past history of urinary tract infection ($OR=1.21$, 95% $CI:0.59-2.34$) was not a significant risk factor. Multivariate analysis showed that age was not a confounder for the association between stress, family history and rheumatoid arthritis.

Conclusions: Stress and a family history of the disease are significant risk factors of rheumatoid arthritis. These associations are not confounded by age.

Introduction

Rheumatoid arthritis is a systemic disease, which involves the mesenchymal connective tissues at a wide variety of sites, usually presenting as a chronic inflammatory polyarthritis, which may lead to disability and handicap (1). Enhanced knowledge on various aspects of the disease has in turn led to large-scale improvements in the methods of treatment. However, the aetiology and mechanisms of pathogenesis remain obscure and continue to present a challenge to contemporary medicine.

¹ Asst. Epidemiologist, Epidemiological Unit, Dept. of Health Services, Sri Lanka.

² Consultant, Ministry of Health, Gaborone, Botswana.

³ Professor of Community Medicine, Faculty of Medicine, University of Colombo, Sri Lanka.

A few studies on the role of psychological factors and several studies in search of genetic factors and possible infective aetiology in the development of rheumatoid arthritis have been conducted (2-8). A link between preceding psychosocial stress and illness has been recognised for a considerable period of time (9). Significant life events or life changes, by altering the life pattern of an individual bring about stress and has been associated with an increased risk of disease (10, 11).

Although the aetiology of rheumatoid arthritis remains unknown, there is a body of opinion that considers it to be multifactorial with environmental and genetic factors playing an important role. Of the environmental factors, investigative efforts have been made to implicate bacteria in the pathogenesis of rheumatoid arthritis, and research has indicated that the urinary tract pathogen *Proteus* may be incriminated (12, 13). Rheumatoid arthritis does not appear to segregate in families in a direct Mendelian fashion. However, the association of the disease with genes within the major histocompatibility complex of chromosome 6 (14) and the results of twin concordance studies (15) provide evidence of the involvement of genetic factors in the aetiology of rheumatoid arthritis.

The objective of our study was to ascertain the association of three risk factors, namely, stress, urinary tract infection and a family history of the disease, with the development of rheumatoid arthritis. We conducted a case-control study for this aetiological inquiry.

Methods

The study was done at the National Hospital Sri Lanka and the Colombo South Teaching Hospital, both of which conduct daily rheumatology and surgical clinics. We selected the cases from patients attending the two rheumatology clinics at the respective hospitals. Preliminary investigations revealed that males constituted only a small percentage (<10%) of rheumatoid arthritis patients attending these clinics. Therefore, the study was limited to female patients, seen by the respective rheumatologist. The sample size was calculated for varying confidence intervals, power of study and probabilities of exposure in the control group, so as to ascertain a feasible sample. At a probability of 50% exposure in the control group, with a study power of 80% and at the 95% significance level, a sample size of 106 cases and 212 controls was selected to estimate an odds ratio (OR) of 2.

Inclusion criteria for cases.

1. Female patients diagnosed as rheumatoid arthritis by the consultant, according to the 1988 Revised American Rheumatism Association criteria.
2. Onset of the disease within the past five years - The onset of the disease was determined by eliciting information from the patient regarding the date or period of the first joint symptom. Pain, swelling or limitation of movement of the joints were the relevant initial symptoms
3. Patients above the age of 20 years - This was to exclude juvenile rheumatoid arthritis (JRA) cases. The risk factors of JRA are likely to be different from those of rheumatoid arthritis.

Cases, which satisfied the inclusion criteria, were enrolled into the study until the stipulated sample was obtained. Due to the paucity of eligible cases, a random sampling technique was not used.

The controls were selected from a variety of conditions presenting to the surgical and ENT clinics of the two hospitals, and had been seen by a consultant. Corresponding numbers of cases and controls were chosen from the two hospitals, thus ensuring indirect comparability with respect to their socio-economic status and other environmental factors.

Exclusion criteria for controls

1. Patients with a past or present history of any musculo-skeletal disorder.
2. Onset of the initial symptoms of the respective disease more than five years prior to the study.
3. Patients below the age of 20 years.

A systematic sampling technique was adopted in selecting the controls. The sampling frame was the average number of patients attending the clinic during a session. The first author and three trained interviewers collected information from the cases and controls, at the time of their clinic visit. An interviewer-administered questionnaire was used to elicit basic information about the patient as well as details on the relevant risk factors.

For determining stress, we used a culturally adapted version of the Social Re-adjustment Rating Scale (SRRS) of Holmes and Rahe (16) in this study. It is a list of 41 life events which individuals may have experienced during a given period prior to the onset of the disease. As different amounts of stress are inherent in different events, a mean value has been calculated for each event. The respondents were requested to recall the various events, which occurred during the 2-year period prior to the onset of the disease. The mean values corresponding to the events experienced were then totalled to

produce a Life Change Unit (L.C.U.) score, which was related to subsequent disease.

One or more episodes of urinary tract infection satisfying laid down criteria, within a 1-year period preceding the onset of the disease was regarded as positive. A quasi-retrospective method was used to identify a positive family history of rheumatoid arthritis. A history of the disease in the subject's first and second-degree relatives was considered as evidence of prior exposure to genetic factors.

Results and analysis

Analysis of the data was carried out manually and with the aid of microcomputers. The software packages used for the computer data analysis were FoxPro, SPSS/PC+, EPI-Info and GLIM.

Among the controls, the highest percentage was multinodular physiological goitres, which accounted for 26% of controls. Solitary nodules of the thyroid and otitis media were 20% and 13% respectively. The age distribution of cases and controls is given in Table 1. The highest percentage of cases and controls were in the 40-49-year age group. Thirty nine percent of cases were over 50 years while in the controls it was 17%. The mean age of cases was 46.7 years (SD: 10.39) and 39.2 (SD: 10.15) the controls ($t=6.22$, $P<0.001$). Seventy five percent of cases and 84% of controls had an education up to grade 6 and above. There was no statistically significant difference between cases and controls in relation to ethnicity, religion, and marital status.

Table 1. Age distribution of cases and controls.

Age (in years)	Case No.	Case %	Control No.	Control %	Total No.	Total %
20-29 years	7	6.6	43	20.3	50	15.7
30-39 years	18	17.0	63	29.7	81	25.5
40-49 years	40	37.7	70	33.0	110	34.6
50-59 years	27	25.5	30	14.2	57	17.9
60+ years	14	13.2	6	2.8	20	6.3
Total	106	100.0	212	100.0	318	100.0

The number and percentage of cases and controls who experienced individual life events according to the Holmes and Rahe scale, in the 2-year period preceding the onset of the respective diseases were analysed. Of the 41 life events in the scale, the event giving rise to the highest stress score is the death of a spouse. Eleven percent of cases had experienced this event in contrast to 3% of the controls. Twenty-seven of the 41 life events occurred more frequently in cases than in the controls. Conversely, 12 events occurred more frequently in controls, with 2 of them equally

distributed. The SRRS categorises stress into high, medium and low levels depending on different cut off points. Table 2 depicts the distribution of cases and controls by the total stress (L.C.U. score). A high stress score (>200) was obtained by 38% of cases in contrast to 17% of controls. Based on the mean stress score of the sample population, stress was then categorised into high and low levels. Seventy one percent of cases had a high stress score as opposed to 40% of the controls. (OR=3.61, 95% CI: 2.13-6.16). The difference between the mean stress score of the cases (187.2) and controls (137.4) was statistically significant. ($t=5.42$, $P<0.01$). An analysis of variance (ANOVA) test was performed, the results of which showed that age and stress scores were not significantly associated. ($P>0.05$).

Table 2. Distribution of cases and controls by the total stress score (L.C.U. score).

Total stress score (L.C.U. score)	Case		Control		Total	
	No.	%	No.	%	No.	%
<100 (low stress)	14	13.2	70	33.0	84	26.4
100-200 (mod. stress)	52	49.1	106	50.0	158	49.7
>200 (high stress)	40	37.7	36	17.0	76	23.9
Total	106	100.	212	100.	318	100.
		0		0		0

The number and percentage distribution of cases and controls by the occurrence of a urinary tract infection, during the preceding 1-year prior to disease, is depicted in Table 3. Accordingly, 16% of cases and 14% of controls had a preceding urinary tract infection, which was not significantly different. (OR=1.21, 95% CI: 0.59-2.34).

Table 3. Distribution of cases and controls by the occurrence of urinary tract infection.

Urinary tract infection	Case		Control		Total	
	No.	%	No.	%	No.	%
Yes	17	16.0	29	13.7	46	14.5
No	89	84.0	183	86.3	272	85.5
Total	106	100.0	212	100.0	318	100.0

The distribution of cases and controls by their family history of rheumatoid arthritis is given in Table 4. This table illustrates that 37% of cases and 10% of controls had a family history of the disease. (OR=5.03, 95% CI: 2.66-9.55).

Table 4. Distribution of cases and controls by their family history of rheumatoid arthritis.

Family history of rheumatoid arthritis	Case		Control		Total	
	No.	%	No.	%	No.	%
None	67	63.2	190	89.6	257	80.8
1st degree family	32	30.2	17	8.0	49	15.4
2nd degree family	6	5.7	5	2.4	11	3.5
Both above	1	0.9	0	0.0	1	0.3
Total	106	100.0	212	100.	318	100.
				0		0

Note: Member of the first-degree family denotes the parents and siblings of the proband. Member of the 2nd degree family denotes the grandparents, uncles and aunts.

In the univariate analysis age, family history and stress were found to be significant risk factors of rheumatoid arthritis. Using the GLIM programme we fitted a logistic regression model by adding each variable, one by one. Deviance analysis was the main criteria used to decide the significance of each item. In the best fit logistic model, age, family history and stress were significant risk factors of rheumatoid arthritis, whereas urinary tract infection was not. This suggests that age is not a significant confounder for the association between stress and family history with rheumatoid arthritis.

Discussion

The objective of this study was to ascertain the association of three risk factors, namely, preceding stress, urinary tract infection and a family history of the disease with the development of rheumatoid arthritis. Rheumatoid arthritis is a relatively rare disease with an overall prevalence of about 1% (17). Mantel and Haenszel described the case-control method as the research strategy of choice in investigating rare diseases. It permits the investigation of multiple hypotheses regarding the causal factors of the disease (18). Certain disadvantages are however inherent in the case-control methodology. For instance the difficulties encountered in selecting an appropriate control group and the possibility of bias, could distort the estimation of the association between cause and effect.

Many hospital based case-control studies use patients with other diseases to constitute the control group. If the control group consists of persons with one particular disease, the control disease may in

fact be related either positively or negatively to the exposure/s under study and may obscure the relationship (19). Our study utilised a wide variety of surgical and E.N.T. patients, who are unlikely to share the same risk factors. The use of hospital controls, as in the present study, would minimise recall bias. However, the possibility that the cases are able to recall some factors better than the controls does remain. This may have occurred due to the fact that the rheumatoid arthritis patients might have repeatedly been questioned on some of its etiological factors. But as some of the factors investigated in this study are not usually ascertained by medical officers, the extent of this bias is considered minimal.

Rheumatoid arthritis is a chronic disease, the pathogenesis and early manifestations of which remain unclear. Therefore, the possibility exists that the onset of the disease may actually precede the exposure/s under study. This temporal confusion may result when the early manifestations of the disease cause a change in the pattern of exposure in cases. Rheumatoid arthritis can be a source of many social and emotional problems. Hence, an exposure like stress may be spuriously labelled as a causal factor. Appreciating this fact, every effort was made in the interview to ascertain the events which occurred prior to the first symptoms.

In this study, the stress scores were categorised into high and low stress groups, based on the mean stress score of the sample. The OR of 3.61 with a significant confidence interval suggests that a relationship exists between major life events experienced by an individual and the subsequent development of rheumatoid arthritis. This concurs with the findings of previous studies which have reported an association between stressful life events and subsequent disease (9, 10). It also supports the findings of other studies which have related stress to the onset of rheumatoid arthritis (2, 20). The SRRS of Holmes and Rahe was used in this study. Such scales may be considered inadequate to measure a concept as complex as stress in an individual. Hence, the effect of minor 'hassles' may also need to be considered in relation to health (21).

Our study indicates that the occurrence of a urinary tract infection, in the year immediately preceding the onset of disease, is not a risk factor of rheumatoid arthritis (OR=1.21, 95% CI: 0.59-2.43). Different studies in pursuit of an association between *Proteus* infection of the urinary tract and rheumatoid arthritis have produced conflicting results (3, 22, 23). We sought a past history of an urinary tract infection as evidence of an infection with *Proteus*. However, urinary tract infection may be caused by many other organisms, and even in the case of a *Proteus* infection, the patient may

remain asymptomatic. Further, the occurrences of mild urinary infections may not be recollected by the patient.

This study revealed a strong relationship between a family history of rheumatoid arthritis and the development of the disease (OR=5.03, 95% CI: 2.66-9.55). The findings concur with the findings of previous studies which indicate the importance of family history in the development of rheumatoid arthritis (4,5). However, it has been shown that family information bias may play a role in the ascertainment of the family history of a patient. Schall and Cobb demonstrated that family history of a disease vary markedly depending upon whether the individual providing the information had the disease or not (24). This in turn may have played a part in the highly significant OR. The increased occurrence of the disease in relatives of cases may also be due to common environmental exposure. However, the genetic contribution to the aetiology of rheumatoid arthritis is strongly suggested by this study.

This was an unmatched case-control study. Attempts were made in the stage of analysis to assess the confounding factors. Age is considered a universal confounding factor. Stratified analysis and fitting of a logistic model revealed that age did not confound the exposure-disease relationship. However, the possibility of other unrecognised confounders need to be taken into account in assessing the results of this study.

Acknowledgements

We wish to thank the consultant rheumatologists Dr. Mrs. T.S. Vidyasagara, Dr. J.V. Aryasinghe, Dr. L. Wijeyaratne and Dr. Mrs. A. Herath for their assistance and guidance during the study; the consultant psychiatrists Prof. D. Samarasinghe and Dr. Mrs. H. Perera for their useful comments and Dr. Ananda Nimalasuriya of the University of California and Prof. Anthony Anghie of the University of Utah, U.S.A., for their generous assistance with regard to literature.

References

1. Cobb S. *The frequency of rheumatic disease*. Massachusetts: Harvard University Press, 1971.
2. Darwish M, Armenian HK. A case-control study of rheumatoid arthritis in Lebanon. *International Journal of Epidemiology*. 1984;16:420-424.

3. Dowlatsbahi D, Paykel ES. Life event and social stress in puerperal psychosis: Absence of effect. *Psychological Medicine*. 1990;20:655-662.
4. Silman AJ, Hennessy E, Ollier B. Incidence of rheumatoid arthritis in a genetically predisposed population. *British Journal of Rheumatol*. 1992;31:365-368.
5. McDonagh JE, Walker DJ. Incidence of rheumatoid arthritis in a 10-year follow-up study of extended pedigree multicase families. *British Journal of Rheumatology* 1994;33:826-831.
6. Deighton C, Heslop P, McDonagh J, et al. Does genetic anticipation occur in familial rheumatoid arthritis? *Annals of Rheumatoid Disease*. 1994;53:833-835.
7. Venables PJW. Infection and rheumatoid arthritis. *Curr Op Rheumatol*. 1989;1:15-20.
8. Hughes RA. The microbiology of chronic inflammatory arthritis. A historical review. *British Journal of Rheumatol*. 1994;33:361-369.
9. Cooper CL, Cooper R, Faragher EB. Incidence and perception of psychological stress: The relationship with breast cancer. *Psychological Medicine*. 1989;19:415-422.
10. Davidson GC, Neale JM. *Abnormal Psychology*, 5th edition, USA : John Wiley and Sons, 1990.
11. Ratkin JG, Streuning EL. Life events, stress and illness. *Science*. 1976;194:1013.
12. Ebringer A, Khalafpour S, Wilson C. Rheumatoid arthritis and *Proteus*. A possible etiological association. *Rheumatology International* 1989;9:223-228.
13. Deighton CM, Gray JW, Bint AJ, Walker DJ. Anti *Proteus* antibodies in rheumatoid arthritis same-sexed sibships. *British Journal of Rheumatol*. 1992;31:241-245.
14. Kingsley G, Panayi G. The immune pathogenesis of rheumatoid arthritis. *British Journal of Rheumatology* 1991;30:3-9.
15. Silman AJ, MacGregor AJ, Thompson W, et al. Twin concordance rates for rheumatoid arthritis: Results from a nation wide study. *British Journal of Rheumatology* 1993;32:903-907.
16. Holmes TH, Rahe RH. The Social Readjustment Rating Scale. *Journal of Psychosomatic Research*. 1985;11:213-218.
17. Hazes JMW, Silman AJ. Review of UD data on the rheumatic diseases - 2, rheumatoid arthritis. *British Journal of Rheumatology* 1990;29:310-312.
18. Schlesselman J. *Case-control studies : designed, conduct analysis*, New York: Oxford University Press 1982.
19. Pearce N, Chekaway H. Case-control studies using other diseases as controls: Problems of excluding exposure related diseases. *American Journal of Epidemiology* 1988;127:851-856.
20. Baker GHB. Life events before the onset of rheumatoid arthritis. *Psychother Psychosom*. 1982;38:173-177.
21. Baron RA, Byrne D, Suls J. *Exploring abnormal psychology*. Massachusetts 3rd edition: Allyn and Bacon USA, 1989.
22. Wilson C, Corbett M, Ebringer A. Increased isolation of *Proteus mirabilis* species in rheumatoid arthritis patients compared to osteo-arthritis patients and healthy controls. *British Journal of Rheumatology* 1990;29(Suppl.2):99.
23. McDonagh J, Gray J, Sykes H, et al. Anti *Proteus* antibodies and *Proteus* organisms in rheumatoid arthritis: A clinical study. *British Journal of Rheumatology* 1994;33:32-35.
24. Schall WJ, Cobb S. The intrafamilial transmission of rheumatoid arthritis. *Journal of Chronic Disease* 1969;22:217-22.