Rheumatol Int (2004) 24: 267–271
DOI 10.1007/s00296-003-0369-1

ORIGINAL ARTICLE

E. Kaptanoglu · I. Akkurt · Ö. Sahin · S. Hocaoglu
V. Nacitarhan · H. Elden · E. Serhan

Prevalence of atopy in rheumatoid arthritis in Sivas, Turkey. A prospective clinical study

Received: 14 January 2003 / Accepted: 24 June 2003 / Published online: 2 October 2003
© Springer-Verlag 2003

Abstract Assumed mutual antagonism of T-helper cell (Th)1 and Th2 diseases suggests that the prevalence of atopy should be decreased in rheumatoid arthritis (RA). We tried to determine that prevalence. Sixty-two patients with RA and 61 with osteoarthritis (control group) were included in the study. A questionnaire was used concerning mainly the symptoms of atopy. Skin prick tests, pulmonary function tests, chest X-rays, immunoglobulin E levels, and eosinophil counts were obtained. The prevalences of asthma, hay fever, and eczema in the RA group were 3.2%, 14.5%, and 1.6%, respectively. In the control group, they were 6.5%, 22%, and 6.5%, respectively. There was no significant difference between groups. There was also no significant difference between immunoglobulin E levels. Eosinophil counts were higher in the control group, however these values were within the normal range. Skin prick tests were obtained in seven RA patients, and eight controls revealed increased positivity. The prevalence of atopy in rheumatoid arthritis was not different from that in the general population. Our study results cannot support the concept of Th1/Th2 mutual antagonism.

E. Kaptanoglu · Ö. Sahin · S. Hocaoglu · V. Nacitarhan
H. Elden
Department of Rheumatology,
Cumhuriyet University Faculty of Medicine, Sivas, Turkey

I. Akkurt
Department of Chest Diseases,
Cumhuriyet University Faculty of Medicine, Sivas, Turkey

E. Serhan
Department of Rheumatology, New Cross Hospital,
Wolverhampton, U.K.

E. Kaptanoglu (✉)
PK 702, 58141 Sivas, Turkey
E-mail: ekaptan@cumhuriyet.edu.tr
Tel.: +90-542-4148414

Keywords Allergic rhinitis · Asthma · Atopy · Eczema · Hay fever · Rheumatoid arthritis

Introduction

It is well known that T cells are among the regulatory cells of the immune system. T-helper (Th)1/Th2 division has been a useful concept in which Th1 cell activity is important in cellular immunity and Th2 cell activity is necessary for humoral responses. The balance between them is also crucial for a healthy immune response. In autoimmune diseases, this balance is always lost, as in rheumatoid arthritis (RA), in which Th1 cell activity predominates [1]. This is also true for atopic diseases, in which Th2 cell responses predominate [2]. Faced with this evidence, it is highly unlikely that RA and atopy would be seen together, as the two diseases require different pathological mechanisms or might have mutually protective roles.

This hypothesis unfortunately has not attracted much attention so far. Few studies relied mainly on questionnaires, and they are not supported by laboratory investigations. Moreover, there is serious disagreement and contradiction among the results. In this study we tried to determine whether the prevalence of atopy is really decreased in RA, as expected.

Patients and methods

This prospective clinical study was conducted from January 2001 till September 2002. In it, 123 clinic patients were recruited. Sixty-two consecutive patients with RA (mean age 49.8 ± 10.6 years), 54 of them female, constituted the first group, and the remaining 61 patients (mean age 48.6 ± 11.1 years) with degenerative joint disease formed the control group, of whom 55 were female. Patients were matched for age and sex. They all resided within the boundaries of the Turkish city Sivas and were genetically unrelated. Diagnosis of RA was made according to the 1987 American College Rheumatology revised criteria [3]. Detailed history of the

rheumatoid disease was taken; duration of disease, onset age, and drug history were noted. In order to determine the prevalence of atopy, various tests and questionnaire forms were applied to all cases in both groups. The questionnaire was adapted from a standard form, mainly searching for atopic conditions related to the respiratory system, used in previous similar studies [4]. The questionnaires were completed by the patients under the supervision of a specialist from the rheumatology department. For illiterate patients, the questions were read and the form was completed with the help of the specialist.

Investigations included full blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), and total immunoglobulin E (IgE) levels, which were determined by the nephelometric method (Space, Italy) with an Alfa Wassermann kit, and results were expressed as IU/ml (normal range 0–100) in all RA and control cases. Complete blood count was also obtained for both groups, and eosinophil counts were recorded as percentages (normal range 0–7%). Posterior-anterior (PA) chest X-rays in both groups were obtained by standard technique and evaluated by two specialists in chest disease and radiology. Each specialist evaluated the X-rays alone and blindly regarding diagnosis. The PA chest X-rays were grouped according to pathology as follows: 0 normal, 1 diaphragm, 2 mediastinal, 3 hilus, 4 parenchymal, 5 bone and soft tissue, 6 interstitial lung, and 7 combined (1 + 2 + 3 + 4). In addition, detailed pulmonary function tests (PFT) were performed in RA patients and controls. Forced vital capacity (FVC) was obtained for each subject by flow-sensitive spirometry (Vmax29, Sensormedics, USA). First of all, each subject was informed about this maneuver, of which the best of three performances was recorded with patients in a settled position and their noses clamped. The absolute and percentage values of FVC, forced expiratory volume of the 1st s (FEV1), FEV1/FVC, and forced expiratory flow at 25–75% of the flow rate were evaluated, and the pathologies were grouped as follows: normal, obstructive, restrictive, combined (obstructive + restrictive), or small airway involvement [5, 6].

The skin prick test was performed in patients with atopic symptoms as determined by the questionnaire. For this, we preferred patients under the age of 40 years [7]. Those on steroid therapy were excluded from the test, as steroids inhibit cell-mediated hypersensitivity. The RA patients and controls were tested using reagents purchased from Stellergence, France. Responses to a standard of 34 allergens were assessed.

For statistical evaluation, version 10.0 of the SPSS package program was used. Chi-squared test, Fischer's exact test, and unpaired Student's *t*-test were used for comparing variables of the groups, whereas the Mann-Whitney U test was used as a non-parametric test. Correlations of variables were also sought. This study was approved by the Cumhuriyet University Faculty of Medicine ethics committee.

Results

There were 62 RA and 61 control patients, and the groups were comparable regarding age and sex. In the RA group, 48% of the patients were illiterate, and their ratio was 26% in the control group. This difference was statistically significant ($P = 0.004$).

There was no significant difference between groups involving parameters which might have affected the symptoms of atopy such as area of the home, room count, and number of people living in the home. The two groups were also comparable in parameters related to smoking and numbers of housepets ($P > 0.05$).

The results of the atopy symptoms in both groups are shown in Table 1. There was a significant difference between RA and control groups in the parameters "wheezing" ($P = 0.025$) and "wake up with cough within the last year" ($P = 0.043$). The prevalences of asthma, hay fever, and eczema were 3.2%, 14.5%, and 1.6%, respectively, in the RA group and 6.5%, 22%, and 6.5%, respectively, in the control group, with no significant difference between the groups ($P > 0.05$). When only the RA patients with active disease ($n = 44$) were compared to the control group according to ESR and CRP values, wheezing was significantly increased in the RA group ($P = 0.014$).

The IgE levels were slightly above the normal range in the RA group (140.7 ± 192.0 IU/ml), however there was no statistically significant difference between IgE levels of the groups (103.3 ± 160.3 IU/ml in controls) ($P > 0.05$). Eosinophil counts in both groups ($0.89 \pm 0.9\%$ in RA vs $1.95 \pm 1.8\%$ in controls) ranged within normal limits, but the mean value was significantly higher in the control group ($P = 0.001$). There was

Table 1 Comparisons of atopy symptoms between the RA ($n = 62$) and control ($n = 61$) groups, active RA ($n = 44$) and control ($n = 61$) groups, and patients with normal ($n = 80$) and elevated ($n = 35$) IgE

Questionnaire parameter	*N* RA, *n* controls, *P*			*N* active RA, *n* controls, *P*			*N* normal IgE, *n* elevated IgE (> 100 IU/ml), *P*		
Wheezing	11	3	0.025*	9	3	0.014*	9	5	0.758
Wheezing + dyspnea	8	3	0.121	7	3	0.090	7	4	0.733
Wheezing without upper airway infection	6	4	0.743	5	4	0.487	7	3	1.0
Chest tightness during the last year	5	4	1.0	4	4	0.717	5	4	0.452
Wake up with shortness of breath during the last year	3	5	0.491	3	5	1.0	7	1	0.432
Wake up with cough during the last year	10	3	0.043*	9	3	0.014	7	4	0.733
Asthma attack within the last year	0	1	0.496	0	1	1.0	1	0	1.0
Lifetime asthma attack	1	4	0.207	1	4	0.396	2	3	0.164
Physician-diagnosed asthma	2	4	0.439	2	4	1.0	4	2	1.0
Allergic rhinitis	9	14	0.230	5	14	0.128	15	7	0.875
Atopy in 1st-degree relatives	11	5	0.116	6	5	0.520	8	8	0.082
Eczema	1	4	0.207	1	4	0.396	5	0	0.321

*$P < 0.05$

a positive correlation between ESR and CRP ($r = 0.559$, $P = 0.000$) and between IgE levels and RF titers ($r = 0.351$, $P = 0.009$).

Symptoms of atopy were also evaluated regarding IgE levels. Atopy symptoms were compared between patients with normal values and those with elevated values. The diagnoses were not taken into consideration. There were no significant differences between the two groups in this parameter, as illustrated in Table 1 ($P > 0.05$).

The duration of RA ranged between 1 and 25 years, with a mean of 6.5 ± 6.1 years. Results were also evaluated after the RA patients were divided into two subgroups according to disease duration. Those with disease durations of ≤ 5 years were compared to those with > 5 years regarding symptoms of atopy, and no difference was observed ($P > 0.05$).

Evaluation of the chest X-rays did not show any statistically significant difference between groups ($P > 0.05$). Pulmonary functions could be evaluated in 54 patients and 54 controls, as some of the cases could not be incorporated into the test. With the exception of FVC, in which control values were lower ($P = 0.046$), the rest of the tests showed no significant difference. There were 29 patients on steroid therapy, 50 on disease-modifying drugs, and 13 on nonsteroidal anti-inflammatory drugs.

As the patients over 40 and those on steroid therapy were excluded, the skin prick test could be performed in seven RA patients and eight controls with atopy symptoms. Results were negative in all of the RA patients and positive in five of the controls, and the difference was statistically significant ($P = 0.026$).

Discussion

Allergic rhinitis and asthma are the most common manifestations of atopy, an inherited propensity to respond immunologically to many common allergens that affects 10–30% of the population in developed countries [2, 8]. Among the T lymphocyte subsets, Th2 cells are required for atopic responses. Rheumatoid arthritis requires Th1 cell activity for progression, so it might be speculated that RA patients have decreased prevalence of atopic diseases.

In our study, we looked into the prevalence of atopy in RA and found no significant difference between the RA and control groups. There was an increase in the symptoms of wheezing and waking up with cough during the last year in the RA group which could be related to disease activity. The prevalences of asthma, allergic rhinitis, and eczema in the normal population were reported to be 5–76%, 10–15.9%, and 0.7%, respectively [2, 9, 10]. In our study, the prevalences of asthma, hay fever and eczema were 3.2%, 14.5%, and 1.6% in the RA group and 6.5%, 22%, and 6.5% in the control group. The values were identical to those observed in the general population.

We also selected active cases with RA and compared them with the control group. Despite the expected predominance of Th1-related responses induced by RA disease activity, wheezing was the only significantly different symptom and was higher in the RA group. Comparison after grouping the cases according to normal and increased IgE levels did not result in a significant difference for atopy, either. Disease duration also seemed to have no effect on the symptoms of atopy. Positive results of the skin prick test were much higher in the control group, but these numbers were not large enough to be significant.

The study of Driscoll et al. is one of the earliest on the prevalence of RA in atopy. They found a prevalence similar to that in the general population (0.76%) [11]. They also studied the prevalence of atopy in 40 RA patients, concluding that it was similar to that in the general population, and their hypersensitivity responses as assessed by skin prick test, eosinophil counts, and serum IgE levels were normal in RA patients, as in our study. In another study, the prevalence of bronchial reactivity in RA patients was found to be significantly higher than in controls (18% vs 4%), and PFTs were also significantly lower in RA [12]. An increase in wheezing was also observed in the RA cases in our study. However, we could not support this result by changes in the PFTs. There was no difference in the results of chest X-rays and PFT between the groups. Considering the systemic nature of the RA, which might have affected the respiratory system, even in the absence of atopy this result was a little surprising. The existence of possible environmental factors involving lung and the blinded evaluation might have had some effect on these results. There was also prominent lung involvement in the RA group evaluated by chest X-rays, but this was not supported statistically.

The studies of Hilliquin and Allanore et al. were the first to demonstrate that the occurrence of atopy in RA was much lower than in healthy subjects (3.5% vs 16.2%) [13, 14]. Verhoef et al. supported these findings [15]. They demonstrated that the prevalence of hay fever in RA was around half that in controls (8% vs 15%). Rheumatoid arthritic patients with hay fever showed higher levels of serum IgE and peripheral blood eosinophils than other RA patients without hay fever. They also claimed that RA was less severe when hay fever was present. However, it was stated that seasonal changes reflected by changes in the Th1/Th2 balance did not coincide with further suppression of disease activity in these RA hay fever patients. This controversial finding is in accordance with a recent article stating that, despite the potent anti-inflammatory capacities of two prominent Th2 cytokines in many experimental studies, clinical trials with either human interleukin 4 (IL-4) or IL-10 in RA patients did not lead to substantial disease suppression in RA [16]. These results support our findings and those of Kero et al, who stated that Th1 and Th2 diseases could coexist, indicating a common environmental denominator behind the disease processes. They

found the incidence of asthma in children with RA (10.0%) or celiac disease (24.6%) to be significantly higher than in those without (3.4%) [17]. Moreover, in another recent study, a rather high prevalence of allergic respiratory disease (allergic rhinitis) in RA (16.6%) was documented [18].

On the basis of a mutual Th1/Th2 antagonism, another aspect of the argument can be that the prevalence of atopy is expected to be higher in SLE, a predominantly Th2 cell disease. However, it was found that allergic diseases were significantly less frequent in SLE patients, thus contradicting the expected outcome of Th1/Th2 antagonism [19].

An association between smoking and development of RA has been reported before; however, we could establish no correlation between smoking history of the RA group and the controls. This may be related to the fact that most of our patients were women and thus nonsmokers because of local social and cultural reasons [20]. Most of our RA cases were not educated, whereas the opposite was true for the controls. Some authors believe that the risk of RA decreases with increasing level of education, and our results support this finding [21].

Though there was no significant difference between the RA and control groups, the levels of IgE were above normal ranges in the RA patients. We believe that this increase is not related to atopy but instead reflects the disease activity. Total IgE levels were increased in RA, even in relatives of the patients [22]. Correlations between the RFs of IgE and IgM and between IgE RF and clinical activity of the disease were also stated [23, 24]. We also found a correlation between IgE and RF titers in our RA patients. Thus IgE, the gold standard of atopy, can be misleading in autoimmune diseases, in which increased IgE levels do not always correlate with atopy and high levels do not necessarily bring out atopic symptoms. Instead of total IgE levels, IgE specific for the allergen would give a better result.

The eosinophil counts in both groups were within normal ranges, though there was an increase in the control group. This was surprising, as eosinophils participate in the inflammatory reaction in RA and one would expect eosinophilia. However, it was reported that the RA patients had normal eosinophil blood counts but increased eosinophil functions [25].

The number of studies on the prevalence of atopy in RA is scarce, and their results are controversial. This may be related first of all to differences in the methods used. In most of the studies, responders completed the questionnaires without the help of professional interviewers [13, 14, 21]. This may have caused some under- or overestimation of symptoms. Besides, there were no diagnostic tests such as skin prick test, IgE levels, and eosinophil counts, which provide the most objective means of diagnosing atopic disorders. The symptoms of atopy searched for are also limited in many studies, which mostly chose hay fever; but we took many symptoms into consideration, used a more detailed questionnaire, and supported our results with laboratory investigations. Moreover, in order to minimize possible bias by environmental and genetic factors, we decided to restrict our study to urban Sivas.

In conclusion, our study reveals that the prevalence of atopy in RA was no different from that in the general population.

References

1. Panayi GS, Corrigall VM, Pitzalis C (2001) Pathogenesis of rheumatoid arthritis: The role of T cells and other beasts. Clin North Am 27:317–334
2. Terr AI (1991) The atopic diseases. In: Stites DP, Terr AI (eds) Basic and clinical immunology, 7th edn. Lange, Lebanon, pp 380-399
3. Arnett FC, Edworth SM, Bloch DA et al (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31:315–324
4. Burney PGJ, Luczynska C, Chinn S et al (1994) The European Community Respiratory Health Survey. Eur Respir J 7:954–960
5. American Thoracic Society, Medical Section of the American Lung Association (1987) Standardization of spirometry—1987 update. Ann Rev Respir Dis 136:1285–1298
6. American Thoracic Society (1991) Lung function testing: selection of reference values and interpretative strategies. Ann Rev Respir Dis 144:1202–1218
7. Niemeijer NR, de Monchy JG (1992) Age-dependency of sensitization to aero-allergens in asthmatics. Allergy 47:431–435
8. Barraclough R, Devereux G, Hendrick DJ et al (2002) Apparent but not real increase in asthma prevalence during the 1990s. Eur Respir J 20:826–833
9. Pallasaho P, Lundback B, Meren M et al (2002) Prevalence and risk factors for asthma and chronic bronchitis in the capitals Helsinki, Stockholm and Tallinn. Respir Med 96:759–769
10. Olivieri M, Verlato G, Corsico A et al (2002) Prevalence and features of allergic rhinitis in Italy. Allergy 57:600–606
11. O'Driscoll BRC, Milburn HJ, Kemeny DM et al (1985) Atopy and rheumatoid arthritis. Clin Allergy 15:547–553
12. Hassan WU, Keaney NP, Holland CD et al (1994) Bronchial reactivity and airflow obstruction in rheumatoid arthritis. Ann Rheum Dis 53:511–514
13. Hilliquin P, Allanore Y, Coste J et al (2000) Reduced incidence and prevalence of atopy in rheumatoid arthritis. Results of a case-control study. Rheumatology 39:1020–1026
14. Allanore Y, Hilliquin P, Coste J et al (1998) Decreased prevalence of atopy in rheumatoid arthritis. Lancet 351:497
15. Verhoef CM, van Roon JAG, Vianen ME et al (1998) Mutual antagonism of rheumatoid arthritis and hay fever; a role for type 1/type 2 T cell balance. Ann Rheum Dis 57:275–280
16. van Roon JA, Bijlsma JW, Lafeber FP (2002) Suppression of inflammation and joint destruction in rheumatoid arthritis may require a concerted action of Th2 cytokines. Curr Opin Investig Drugs 3:1011–1016
17. Kero J, Gissler M, Hemminki E et al (???) Could TH1 and TH2 disease coexist? Evaluation of asthma incidence in children with celiac disease, type 1 diabetes, or rheumatoid arthritis: a register study. J Allergy Clin Immunol 108:781–783
18. Provenzano G, Donato G, Brai G et al (2002) Prevalence of allergic respiratory diseases in patients with rheumatoid arthritis. Ann Rheum Dis 61:281
19. Sekigawa I, Yoshiike T, Iida N et al (2002) Allergic disorders in systemic lupus erythematosus: prevalence and family history. Lupus 11:426–429
20. Gabriel SE (2001) The epidemiology of rheumatoid arthritis. Clin North Am 27:269–281
21. Olsson AR, Skogh T, Wingren G (2001) Comorbidity and lifestyle, reproductive factors, and environmental exposures

associated with rheumatoid arthritis. Ann Rheum Dis 60:934–939
22. Meretey K, Gomor B, Gorgenyi F et al (1987) Study of autoantibodies, natural antibodies and IgE level in four families with rheumatoid arthritis. Z Rheumatol 46:189–195
23. Herrmann D, Hein G, Jager L (1993) IgE rheumatoid factors: occurrence and diagnostic significance [German]. Immun Infekt 21 [Suppl 1]:16–17
24. De Clerck LS, Struyf NJ, Bridts CH et al (1989) Humoral immunity and composition of immune complexes in patients with rheumatoid arthritis, with special reference to IgE-containing immune complexes. Clin Exp Rheumatol 7:485–492
25. Hallgren R, Feltelius N, Svenson K et al (1985) Eosinophil involvement in rheumatoid arthritis as reflected by elevated serum levels of eosinophil cationic protein. Clin Exp Immunol 59:539–546