

Risk factors for rheumatoid arthritis: Level of education, tonsillectomy and appendectomy

Romatoid artrit risk faktörleri: Eğitim düzeyi, tonsillektomi ve apendektomi

Mohammad Mahdi EFTEKHARIAN

ABSTRACT

Objective: Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder of flexible joints with unknown etiology, which affects 1% of the world's population. The aim of this 2010 study was to investigate the association between the level of education, tonsillectomy and appendectomy in the patients' history with RA. The study was carried out in Hamedan City, in the West of Iran.

Patients and Methods: As a patient-control study, information from 128 patients and 130 controls, matched for age and gender, was collected by questionnaires and physical exams with the consent of both patients and controls, followed by an SPSS statistical analysis (Pearson's Chi-Square test).

Results: In patient and control groups, there were 116 and 117 females, respectively, and the rest were males. Statistical analysis showed that there is no significant association between level of education or tonsillectomy with RA ($p>0.05$), whereas appendectomy was significantly associated inversely with the risk of RA ($p < 0.05$).

Conclusion: Considering previous global investigations on this topic with different results and the results of our study, it seems that more studies are needed to determine the definitive association between level of education, tonsillectomy and appendectomy with the risk of RA.

Key words: Rheumatoid arthritis, Level of education, Socioeconomic level, Social class, Tonsillectomy, Appendectomy, Risk factors

ÖZET

Amaç: Romatoid artrit (RA) kronik, otoimmün, enflamatuvar ve etiolojisi tam olarak bilinmeyen bir eklem hastalığıdır. Dünya nüfusunun %1'in de görülmektedir. Bu çalışmanın amacı, RA hikayesi olan hastalarda eğitim düzeyi, tonsillektomi ve apendektomi arasındaki ilişkiyi araştırmaktır. Çalışma Batı İran'da Hamedan şehrinde yapılmıştır.

Hastalar ve Yöntem: Çalışma, yaş ve cinsiyet bakımından uyumlu 128 hasta ve kontrol grubunu oluşturan 130 kişi üzerinde yapılmıştır. Hasta-kontrollü çalışmada bilgiler, gruplara anket uygulayarak elde edilmiştir. Fizik muayene, kişilerden izin alınarak yapılmıştır. İstatistiksel analiz SPSS (Pearson's Chi-Square test) ile yapılmıştır.

Bulgular: Hasta grubunda 116, kontrol grubunda ise 117 kadın bulunuyordu. Geri kalanlar erkek idi. İstatistiksel analiz RA riski ile eğitim durumu veya tonsillektomi arasında belirgin bir ilişki olmadığını göstermiştir ($p > 0,05$). Ancak RA riski ile apendektomi arasında belirgin ters bir ilişki elde edilmiştir ($p < 0,05$).

Sonuç: Bu konuda daha önce yapılmış büyük araştırmalardan elde edilen değişik sonuçlar ile bizim araştırmamızdan elde ettiğimiz sonuçlar değerlendirildiğinde, eğitim durumu, tonsillektomi ve apendektomi ile RA riski arasındaki kesin ilişkiye ulaşmak için daha fazla araştırmalara gerek olduğu kanısına varılmıştır.

Anahtar kelimeler: Romatoid artrit, Eğitim düzeyi, Sosyoekonomik durum, Sosyal sınıf, Tonsillektomi, Apendektomi, Risk faktörleri

Introduction

Rheumatoid arthritis (RA) as a chronic autoimmune inflammatory disorder with unknown etiology is one of the most important autoimmune diseases, affecting 1% of the world's population. RA is a form of recurrent chronic arthritis that usually involves several joints symmetrically leading to restriction of activities of daily living and deterioration of the quality of life. RA, similar to other multifarious diseases, is believed to be influenced by both genetic and environmental factors [1-4]. Based on previous studies, the genetic factors are responsible for more than half of the risk of developing RA [2]. However, as in most other complex diseases, few such interactions have been described and it is assumed that

Mohammad Mahdi Eftekharian (✉)
Research Center for Molecular Medicine, Research Center for Neurophysiology
and School of Paramedicine, Hamadan University of Medical Sciences,
Fahmideh Blvd., Hamadan, Iran
e-mail: eftekharian@umsha.ac.ir

Submitted/Gönderilme: 12.11.2012 - Accepted/Kabul: 13.12.2012

more studies will be needed to determine significant and definite gene–environment interactions in these diseases. The main genetic risk factor is the shared epitope (SE) of HLA-DR, but in the context of environmental triggers, several risk factors have been suggested [1-4]. One of the most important of such factors has been the history of particular infections such as Epstein-Barr virus (EBV) [2, 5-7]. Infection of B lymphocytes followed by their polyclonal activation will cause the production of rheumatoid factor (RF). RF is a member of the class of Ig-M autoantibodies that react with auto-Ig-G, and then, precipitate in joints. The appearance of RA following a history of infection has also been attributed to other microorganisms (Microplasma, Cytomegalovirus and Rubella) [2]. As mentioned previously, the incidence rate of RA in the world is about 1% (ranging from 0.3% to 2.1%) and, based on previous studies, women are more susceptible than men [1-4]. Familial studies have also shown that genetic susceptibility is important in this regard and the role of shared epitope of HLA has been proven [1-4]. Several other areas of research on other risk factors have identified coffee consumption [8-10], blood transfusion history [11, 12], gender [1-4, 13], sex hormones [2, 14], diet [2, 15-17], weather [2, 18, 19], smoking [2-4, 20-31], obesity [32], diabetes [33] and family history [33]. To investigate the influence of other factors on the risk of RA in our region, we decided to perform a patient-control study. As mentioned in other reports, 80% of RA patients begin in the fourth and fifth decades of life, and information about relative risk factors and useful instructions should assist in identifying preventive methods and decrease the incidence of RA. Regarding the importance of education in several aspects of life (e.g. exposure to viral infections, smoking or obesity) we thought that a higher level of education might have an indirect protective role in relation to RA. In other words, there might be an inverse relationship between level of education and the risk of RA. Furthermore, since tonsils and appendix are a part of the peripheral immune organs (with unknown definitive functions) and the etiology of RA is originally related to defective functions of the immune system, it is expected that there might be an association between a history of tonsillectomy and / or appendectomy and a risk of RA. Some researchers have already tried to provide convincing answers to these questions [13, 29, 34-39], but different results relating to different areas of the world demonstrate that geographically limited studies cannot be generalized to other parts of world because some known and unknown area-dependent factors may have an effect. Since, there were not any convincing definitive reasons for accepting or rejecting the possible associations between level of education, tonsillectomy and the appendectomy history with RA, in 2010, we started to investigate any association between these factors and a history of RA in Hamadan, a city located in the West of Iran.

Patients and Methods

Design of study

This research was designed as a patient-control study involving the incidence of RA in the population, aged 20–55 years, in a geographically defined city in the Western part of Iran, Hamadan. The recruitment period for the patients and controls was 2010.

Selection of the patients and controls

All referring potential patients were examined and diagnosed by a rheumatologist in Mobasher Hospital, the centre of rheumatology care in Hamadan. A definite RA diagnosis was completed for 128 individuals after an RA latex examination of blood samples, physical exam, clinical symptoms and a study of the personal history. A primary analysis was then conducted in order to calculate the averages for gender and age in the patient group. A total of 130 control subjects was then selected by physicians among healthy persons matched for age and sex with the patient group.

Data collection

All needed data about the level of education, tonsillectomy and appendectomy history were collected by a standard questionnaire and a physical exam in the presence of a physician with the consent of both patients and controls.

Statistical analysis

The statistical analysis was performed by SPSS version 16 software and using Pearson's chi-square test. P-values lower than 0.05 were considered as a significant result. Results were analyzed and studied using cross-tabulation.

Results

After filling out the questionnaires, the results were statistically analyzed. In the patient and control groups (128 and 130), there were 116 and 117 females, respectively, and the rest were males. The mean age of the patients was 37.51 years and 37.54 for the controls. The association between the level of education and RA, analyzed using Pearson's chi square test gave a P-value of 0.18, meaning there is not a significant relation between the level of education and RA (Table I). Similar results were obtained in other part of our study, which showed that tonsillectomy has no significant association with the risk of RA ($p=0.06$) (Table II). However, appendectomy was significantly and inversely associated with RA ($p=0.04$) (Table III).

Discussion

Education has also been considered as a socioeconomic marker in previous studies in different areas of the world. The first part of results of the present study show that there is no

Table I. Cross-Tabulation between level of education and RA.

Studied groups	Patients		Controls		Total		P.Value
	Number	Percent	Number	Percent	Number	Percent	
Illiterate	37	29.1	27	20.8	64	24.9	0.18 Non-significant
Less than high school diploma	52	40.9	53	40.8	105	40.9	
High school diploma	25	19.7	26	20	51	19.8	
Academic	13	10.2	24	18.5	37	14.4	
Total	127	100	130	100	257	100	

Table II. Cross-Tabulation between tonsillectomy and RA.

Studied groups	Patients		Controls		Total		P.Value
	Number	Percent	Number	Percent	Number	Percent	
Without tonsillectomy	124	96.9	119	91.9	243	94.2	0.06 Non-significant
With tonsillectomy	4	3.1	11	8.5	15	5.8	
Total	128	100	130	100	258	100	

significant association between the level of education and the risk of RA in Hamedan city, in Western Iran. In another study by Vlieland et al. in 1994 [38] on 138 women who attended the outpatient clinic of the Department of Rheumatology of the Leiden University Hospital consecutively, a low educational level was found to be associated with an increase in the severity of RA. They reported that patients with lower levels of education showed a trend towards a worse outcome of RA, and the differences in severity of RA between patients with different levels of education, develop or are present at early stages of the disease. Olsson et al. in 2001 [29], in a retrospective study from 1980 to 1995 and in 2004 [39], both of them in Sweden, showed that the risk for RA decreased with increased levels of education. In other words, higher education seems to have a protective effect on the occurrence of RA. Contrary to these results, Uhlig et al. in 1999 [35], showed that low levels of formal education were not significantly associated with a risk of RA. Based on another study by Jawaheer et al. in 2006 [13] on 1004 affected members of 467 Caucasian multi-patient RA families recruited from the North American Rheumatoid Arthritis Consortium, patients with less education developed RA later in life but had more severe symptoms compared with those with more education. As we see, despite the multiplicity of studies in the context of the relation between educational level and RA, particularly in the European and Scandinavian countries, the results remain controversial. The partially protective effect of high levels of education against RA can be attributed to protective factors, possibly found in the lifestyle and occupations of subjects

with a higher socioeconomic level. In the other part of our study, we found that there is a significant reverse association between appendectomy and risk of RA. It means that appendectomy may have a protective role on RA occurrence, whereas, as shown in table III, tonsillectomy has a borderline reverse association with RA. Linos et al. in 1986 [36] based on a study of 229 female patients compared with 458 controls showed that there is not any significant association between appendectomy or tonsillectomy and the risk of RA. In 1994 and 1983, similar results were obtained by Moens et al. [37] in the Netherlands and Wolfe et al. [40]. As a contrary report, Fernandez-Madrid et al. in 1985 [41], after a patient-control study, found that antecedent removal of lymphoid tissue from the tonsils, adenoids and appendix would be a risk factor predisposing to RA. Moreover, it seems that this risk is related to the quantity of lymphoid tissue removed.

As a conclusion, despite the multiplicity of studies and due to the frequent contradictions in their results, which may be attributed to methodological and/or geographical differences and/or of an unknown nature, it seems that more studies are needed to determine the definitive association between level of education, tonsillectomy and appendectomy with the risk of RA. One of the most important limitations mentioned refers to the nature of patient-control studies. In this case, a definite answer for a causal relationship can never be given. Another limitation concerns to the small sample size of our study. If we were able to increase the sample size, the borderline reasons might be changed as significant associations.

Table III. Cross-Tabulation between appendectomy and RA.

Studied groups	Patients		Controls		Total		P.Value
	Number	Percent	Number	Percent	Number	Percent	
Without appendectomy	124	96.9	118	90.8	242	93.8	0.04 Significant
With tonsillectomy	4	3.1	12	9.2	16	6.2	
Total	128	100	130	100	258	100	

References

- Kallberg H, Padyukov L, Plenge RM, et al. Gene-gene and gene-environment interactions involving HLA-DRB1, PTPN22, and smoking in two subsets of rheumatoid arthritis. *Am J Hum Genet* 2007; 80:867-75. doi: 10.1086/516736
- Kobayashi S, Momohara S, Kamatani N, Okamoto H. Molecular aspects of rheumatoid arthritis: Role of environmental factors. *The FEBS J* 2008;275:4456-62. Doi: 10.1111/j.1742-4658.2008.06581.x
- Padyukov L, Silva C, Stolt P, Alfredsson L, Klareskog L. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of sero-positive rheumatoid arthritis. *Arthritis Rheum* 2004;50:85-92. doi:10.1002/art.20553
- Stolt P, Bengtsson C, Nordmark B, et al. Quantification of the influence of cigarette smoking on rheumatoid arthritis: Results from a population based case-control study, using incident cases. *Ann Rheum Dis* 2003;62: 835-41. doi: 10.1136/ard.62.9.835
- Balandraud N, Meynard, JB, Auger I, et al. Epstein-Barr virus load in the peripheral blood of patients with rheumatoid arthritis: Accurate quantification using real-time polymerase chain reaction. *Arthritis Rheum* 2003;48:1223-8. doi: 10.1002/art.10933
- Balandraud N, Roudier J, Roudier C. Epstein-Barr virus and rheumatoid arthritis. *Autoimmun Rev* 2004;3: 362-7. doi:10.1016/j.autrev.2004.02.002
- Posnett DN. Herpes viruses and autoimmunity. *Curr Opin Invest Dr* 2008; 9: 505-14.
- Heliövaara M, Aho K, Knekt P, Impivaara O, Reunanen A, Aromaa A. Coffee consumption, rheumatoid factor, and the risk of rheumatoid arthritis. *Ann Rheum Dis* 2000;59: 631-5. doi:10.1136/ard.59.8.631
- Karlson EW, Mandl LA, Aweh GN, Grodstein F. Coffee consumption and risk of rheumatoid arthritis. *Arthritis Rheum* 2003;48:3055-60. doi:10.1002/art.11306
- Mikuls TR, Cerhan JR, Criswell LA, et al. Coffee, tea, and caffeine consumption and risk of rheumatoid arthritis: Results from the Iowa Women's Health Study. *Arthritis Rheum* 2002;46: 83-91. doi: 10.1002/1529-0131(200201)46:1<83::AID-ART10042>3.0.CO;2-
- Cerhan JR, Saag KG, Criswell LA, Merlino LA, Mikuls TR. Blood transfusion, alcohol use, and anthropometric risk factors for rheumatoid arthritis in older women. *J Rheumatol* 2002;29:246-54.
- Symmons DP, Bankhead CR, Harrison BJ, et al. Blood transfusion, smoking, and obesity as risk factors for the development of rheumatoid arthritis: Results from a primary care-based incident case-control study in Norfolk, England. *Arthritis Rheum* 1997;40: 1955-61. doi: 10.1002/art.1780401106
- Jawaheer D, Lum RF, Gregersen PK, Criswell LA. Influence of male sex on disease phenotype in familial rheumatoid arthritis. *Arthritis Rheum* 2006;54: 3087-94. doi:10.1002/art.22120
- Heikkilä R, Aho K, Heliövaara M, et al. Serum androgen-anabolic hormones and the risk of rheumatoid arthritis. *Ann Rheum Dis* 1996;57: 281-5. doi: 10.1136/ard.57.5.281
- Ariza-Ariza R, Mestanza-Peralta M, Cardiel MH. Omega-3 fatty acids in rheumatoid arthritis: an overview. *Semin Arthritis Rheu* 1998;27: 366-70. doi: 10.1016/S0049-0172(98)80016-4
- Cutolo M, Otsa K, Uprus M, Paolino S, Serio B. Vitamin D in rheumatoid arthritis. *Autoimmun Rev* 2007;7: 59-64. doi:10.1093/rheumatology/ken394
- Okamoto H, Shidara K, Hoshi D, Kamatani N. Anti-arthritis effects of vitamin K(2) (menaquinone-4): A new potential therapeutic strategy for rheumatoid arthritis. *The FEBS J* 2007;274: 4588-94. doi:10.1111/j.1742-4658.2007.05987.x
- Strusberg I, Mendelberg RC, Serra HA, Strusberg AM. Influence of weather conditions on rheumatic pain. *J Rheumatol* 2002; 29: 335-8.
- Vergés J, Montell E, Tomés E, et al. Weather conditions can influence rheumatic diseases. *Proc West Pharmacol Soc* 2004;47:134-6.
- Eftekharian M M, Basiri Z, Mani Kashani KH. A study of the association between smoking and rheumatoid arthritis. *J Smok Cess* 2010;5: 1-6. doi: 10.1375/jsc.5.1.1
- Criswell LA, Merlino LA, Cerhan JR, et al. Cigarette smoking and the risk of rheumatoid arthritis among postmenopausal women: Results from the Iowa Women's Health Study. *Am J Med* 2002;112: 465-71. doi:10.1016/S0002-9343(02)01051-3
- Heliövaara M, Aho K, Aromaa A, Knekt P, Reunanen A. Smoking and risk of rheumatoid arthritis. *J Rheumatol* 1993;20: 1830-5.
- Hutchinson D, Shepstone L, Moots R, Lear JT, Lynch MP. Heavy cigarette smoking is strongly associated with rheumatoid arthritis (RA), particularly in patients without a family history of RA. *Ann Rheum Dis* 2001;60: 223-7. doi:10.1136/ard.60.3.223
- Karlsson EW, Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH. A retrospective cohort study of cigarette smoking and risk of rheumatoid arthritis in female health professionals. *Arthritis Rheum* 1999;42: 910-7. doi:10.1002/1529-0131(199905)42:5<910
- Klareskog L, Stolt P, Lundberg K, et al. A new model for an etiology of rheumatoid arthritis: Smoking may trigger HLA-DR(shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum* 2006;54: 38-46. doi:10.1002/art.21575
- Krishnan E, Sokka T, Hannonen P. Smoking-gender interaction and risk for rheumatoid arthritis. *Arthritis Res Ther* 2003;5:R158-62. doi:10.1186/ar750
- Mattey DL, Hutchinson D, Dawes PT, et al. Smoking and disease severity in rheumatoid arthritis: Association with polymorphism at the glutathione S-transferase M1 locus. *Arthritis Rheum* 2002;46: 640-6. doi:10.1002/art.10174
- Papadopoulos NG, Alamanos Y, Voulgari PV, Epagelis EK, Tsifetaki N, Drosos AA. Does cigarette smoking influence disease expression, activity and severity in early rheumatoid arthritis patients? *Clin Exp Rheumatol* 2005;23:861-6.
- Reckner Olsson A, Skogh T, Wingren G. Comorbidity and lifestyle, reproductive factors, and environmental exposures associated with rheumatoid arthritis. *Ann Rheum Dis* 2001;60: 934-9. doi:10.1136/ard.60.10.934
- Symmons DP. Epidemiology of rheumatoid arthritis: Determinants of onset, persistence and outcome. *Best Practice & Research Clin Rheumatol* 2002;16:707-22. doi:10.1053/berh.2002.0257
- Symmons DP. Environmental factors and the outcome of rheumatoid arthritis. *Best Practice & Research Clin Rheumatol* 2003;17: 717-27. doi:10.1016/S1521-6942(03)00063-9
- Eftekharian M M, Basiri Z, Mani Kashani KH. Obesity and rheumatoid arthritis: results from a case-control study. *New Iraqi J Med* 2011;7: 5-9.
- Eftekharian M M, Basiri Z, Mani Kashani KH. Do diabetes and family history influence the rheumatoid arthritis? results from a case-control study. *Bang J Med Sci* 2011;10: 230-4. doi:10.3329/bjms.v10i4.9492
- Pedersen M, Jacobsen S, Klarlund M, Frisch M. Socioeconomic status and risk of rheumatoid arthritis: a Danish case-control study. *J Rheumatol* 2006;33: 1069-74.
- Uhlir T, Hagen KB, Kvien TK. Current tobacco smoking, formal education, and the risk of rheumatoid arthritis. *J Rheumatol* 1999;26: 1-3.
- Linos AD, O'Fallon WM, Worthington JW, Kurland LT. The effect of Tonsillectomy and Appendectomy on the development of rheumatoid arthritis. *J Rheumatol* 1986;13: 707-9.
- Moens HB, Corstjens A, Boon C. Rheumatoid arthritis is not associated with prior Tonsillectomy or Appendectomy. *Clin Rheumatol* 1994;13:483-6. doi:10.1007/BFO2242947
- Vliet Vlieland TPM, Buitenhuis NA, van Zeben D, Vandenbroucke JP, Breedveld FC, Hazes JM W. Sociodemographic factors and the outcome of rheumatoid arthritis in young women. *Ann Rheum Dis* 1994;53: 803-6. doi:10.1136/ard.53.12.803
- Reckner Olsson A, Skogh T, Wingren G. Aetiological factors of importance for the development of rheumatoid arthritis. *Scand J Rheumatol* 2004;33: 300-6. doi:10.1080/03009740310004748
- Wolfe F, Young DY. Rheumatoid arthritis and antecedent tonsillectomy. *J Rheumatol* 1983;10:309-12.
- Fernandez-Madrid F, Reed AH, Karvonen RL, Granda JL. Influence of antecedent lymphoid surgery on the odds of acquiring rheumatoid arthritis. *J Rheumatol* 1985;12: 43-8.