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Environmental and personal risk factors for the development of rheumatoid arthritis

Środowiskowe i indywidualne czynniki ryzyka rozwoju reumatoidalnego zapalenia stawów

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Key words

rheumatoid arthritis, risk factors, primary health care

Summary

Rheumatoid arthritis (RA) is a systemic, autoimmune, inflammatory disease of unknown etiology, characterized as a progressive disease, leading to joint destruction, physical activity limitation, disability, premature death, and imposes a significant economic burden on patients, family members, and society. While etiology of rheumatoid arthritis is unknown, medical evidences suggest that RA develops more often in individuals with inherited genetic and individual risk factors or exposed to environmental triggers.

The aims of this paper are the present the latest medical data on these risk factors, the identification of the groups of high risk for RA development and the presentation of suggestions for health related, preventive activities in primary health care.

There are many environmental factors, including exposure to tobacco smoke, infections, hormones, dietary factors that, as well as gene-environment interactions have been associated with increased risk for RA. This article presents latest data on the most important environmental, serological and personal risk factors for RA development.

Early identification of risk factors is important part of health care since it provides opportunity for earlier preventive activities, health promotion in individuals at risk of RA development. Presented data on environmental and personal risk factors could be helpful for primary health care doctors, specialists and other people involved in diseases prevention, treatment and promotion of health.

Introduction

Rheumatoid arthritis (RA) is a systemic, autoimmune, inflammatory disease of unknown etiology, characterized as a progressive disease, leading to joint destruction, physical activity limitation, disability, premature death, and imposes a significant economic burden on patients, family members, and society. RA is considered to appear when genetic and environmental factors interact and trigger immunological changes leading to an inflammatory arthritis. The onset of clinical disease occurs when the cumulative action of genetic and environmental factors trigger an auto-aggressive immune response. This asymptomatic period with immune activation phase, in which autoantibodies and inflammatory markers may be found, could evolve to an unclassifiable or undifferentiated arthritis or an arthritis that fulfills the criteria for RA diagnosis.

There has been limited success defining the environmental factors important in developing RA. The immune pathology in adult RA begins many years before clinical symptom. The RA associated autoantibodies as rheumatoid factor (RF) or anti-citrullinated protein antibody (ACPA) may be present many years before the clinical onset of the disease (1). The search for environmental factors is important because RA was reported to be associated with significantly increased mortality. Moreover, in a cohort of older women, the association appeared to be restricted to those with RF positive disease (2).

Environmental risk factors may be divided in modifiable and non-modifiable factors. All of them are identifying individuals with elevated risk of RA, although all preventive activities are mainly focused on eliminating or limiting the impact of the modifiable factors.

Identification of environmental or familial risk factors for development of rheumatoid arthritis could be helpful in early RA diagnosis. Early diagnosis, referral to rheumatologists and early treatment of RA are recommended by European League against Rheumatism (EULAR) (3). These recommendations help to improve long-term outcomes. Presence of RF or ACPA associates with cardiovascular disease (CVD) and mortality among RA onset before 65 years (4). RA is leading to increased mortality as it was shown in literature in longitudinal observational study (5). Cardiovascular mortality could be associated with chronic inflammation determined by C-reactive protein and erythrocyte sedimentation rate (6).

RA incurs high individual, societal and medical costs, all of which should be considered in its management by the treating rheumatologist (EULAR) or other medical professionals involved in RA treatment. According to EULAR recommendations, treatment should be aimed at reaching a target of remission or low disease activity in every patient and methotrexate should be part of the first treatment strategy in patients with active RA. It was known that successful control of disease activity by treatment with methotrexate reduces mortality in RA (7). Patients with long-standing high disease activity are at substantially increased risk of mortality. In patients responding insufficiently to methotrexate and/or other conventional synthetic disease-modifying antirheumatic drugs strategies, biological disease-modifying antirheumatic drugs should be commenced with methotrexate (EULAR). Comparative analysis suggested also that tumor necrosis alpha inhibitors and rituximab seem to be superior to conventional disease-modifying antirheumatic drugs in reducing this risk (8). All these treatment options could be more cost-effective if the RA diagnosis is made in early stage of this disease. Therefore, Information about risk factors for RA development may be helpful for medical professionals involved in RA diagnosis, treatment and comprehensive care.

The aims of this paper are the presentation the latest medical data on environmental and personal risk factors for the development of rheumatoid arthritis, the identification of the groups of high risk for RA development and the presentation of suggestions for health related, preventive activities in primary health care.

Description of the state of knowledge

Cigarette smoking

Case-control study have demonstrated that cigarette smoking is the strongest environmental factor linked with RA (9). Attributable population risk for smoking is reported to be 25% for all RA and 35% for RA with presence of RF or ACPA (10). The association is more stronger for men than for women (11). A dose-response is reported to be between smoking and RA, particularly in people with seropositive RA with persistence of RA risk for many years after smoking cessation (12). In addition, the risk of seropositive RA associated with smoking has been reported to be highest in those who carry the HLA-DRB1 shared epitope (SE) (13). Other recent data suggested decreased responsiveness to therapy in patients with established RA who were smokers and suggested some relationship between disease development and smoking (14).

Strong combined gene-environment effects were observed, with markedly increased risks of ACPA-positive RA in SE homozygotes who were heavy smokers, heavy coffee drinkers or oral contraceptive users compared with SE noncarriers who were not exposed to these environmental risk factors (15).

Cigarette smoking is well-documented environmental factor, which could increase the risk of developing RA and is correlated with symptoms and poor response to therapy (16). One prospective study reported that smoking and overweight increase the risk of arthritis in a cohort of autoantibody--positive individuals (17). In last times, large study (25 455 participants) investigated the association of lifestyle factors with risk of RA. In this study pack-years of smoking were associated with increased risk of RA in men (18).

Periodontal diseases

Recent findings showed that elevated level of circulating RF and ACPA antibodies may be present in the absence of synovitis on knee synovial biopsy and these data provided support for the conception that immunological abnormalities in RA development may be generated outside of the joints (19). As a specific example of association of mucosal inflammation and RA, recent data has reported the relation between established RA and periodontal disease (20). The current hypothesis is that the *Porphyromonas gingivalis*, responsible for citrullination of human peptides, may be responsible for the initiation and development of RA-related autoimmunity (21).

Vitamin D

Vitamin D has pleotropic effects on the immune system, inhibiting pro-inflammatory cytokines, up-regulating anti-inflammatory cytokines and regulating the innate and adaptive immune system through the vitamin D receptor (22). Greater intake of vitamin D may be associated with a lower risk of RA in older women (23). It was also indicated that patients with more active RA have a lower serum vitamin D level (24). Recent meta-analysis of 215 757 participants suggests that low vitamin D intake is associated with an elevated risk of RA development (25).

Obesity

In recent study, obesity was associated with a modest risk for developing RA, but given the rapidly increasing

prevalence of obesity, this may have a significant impact on RA incidence (26).

Hormone use

It was reported that age at menarche ≤ 12 and younger age at menopause were inversely associated with RA risk (27). It was reported that RA incidence rates increased with age and peaked in post-menopausal women (28). From the other hand, exogenous estrogen therapy among post-menopausal women did not reduced RA risk (29).

Oral contraceptive use was reported to be protective against the development of RA (30). Use of oral contraceptives at any time was inversely associated with rheumatoid factor positivity independent of age, education and smoking (31). All these findings indicated that hormonal disturbances could act early in RA-related immune deregulation and oral contraceptive use may be protective and reducing risk for RA development.

Perinatal characteristics and breast feeding

Recent work has suggested that early growth can have long-lasting effects on autoimmune disease. The risk of developing RA may be influenced by early environmental factors such as growth and feeding. High birth weight was positively associated with RA but initiation of breast-feeding during inpatient care was negatively associated with RA (32). Other study also confirmed association of high birth weight with increased risk for RA (33).

Breast feeding was associated with a reduced risk of RA for women who had breast fed for > or = 13 months (34). In other study breast feeding for > 12 months was inversely related to the development of RA and this effect was dose-dependent, with a significant trend toward lower risk with longer duration of breast-feeding (35). Another study showed information that increasing time of breastfeeding increased the risk of RA for breastfeeding ≥ 17 months (36).

Family history

In a Swedish large study involving subjects with RA, standardized incidence ratios (SIR) were calculated as relative risk (RR) of RA in family members of RA patients as compared with RR in those with no affected family members (37). SIRs for RA were 3.0 in offspring of RA-affected parents, 4.6 in siblings, 9.3 in multiplex families (both parent and sibling) and 6.5 in twins. The 3- to 9-fold increased familial risk of RA suggests strong influence of genetic or environmental effects or both. Moreover, this study suggested that having a first degree relative with RA increases RA risk 3- to 9-fold compared to that in the general population suggesting the influence of shared genetic and/or environmental factors.

FDRs without RA demonstrated high prevalences of genetic risk factors and RA-related autoantibodies (38). First degree relatives of RA probands had a higher prevalence of ACPA antibodies than more distant relatives and unrelated controls (39).

Other factors

A case control study from Sweden, the Epidemiologic Investigation of RA reported an association between occupational silica exposure and RA (40). From the other hand, there was no evidence of increased risk of developing rheumatoid arthritis after occupational exposure to silica (41).

Occupational exposure to other factors such as mineral oils (exposure pathways through the lung and skin) was investigated and exposure was associated with increased risk of RF/ACPA RA, but not of seronegative RA (42).

It was reported that there may be association between RA and exposure to traffic pollution in adulthood (43).

Results from prospective cohort study suggested that intake of certain antioxidant micronutrients, particularly β-cryptoxanthin and supplemental zinc, may protect against the development of rheumatoid arthritis (44).

Some studies reported the possible role of fish protein (45) or iron and meat consumption (46) in RA development although the data are mixed.

In large cohort study, lower socioeconomic status is associated with an increased risk of RA (47). This association remains strong even after adjustment for cigarette smoking, suggesting the existence of an important environmental or lifestyle factor associated with lower socioeconomic status. Other study also reported an inverse association of RA risk with higher education, social class (48).

Analysis of long term alcohol consumption showed that women who reported drinking > 3 glasses of alcohol per week had a 52% decreased risk of RA compared with those who never drank (49). Results of meta-analysis of prospective studies indicated that low to moderate alcohol consumption yielded a preventive effect on RA development and provided some evidence of a non-linear relationship between alcohol consumption and risk of RA (50). In this study, subgroup analysis showed that women who had low to moderate alcohol consumption had a 19% reduction in RA risk. It was also concluded that regardless of sex, a consistent low to moderate alcohol consumption for a period of at least 10 years was found to have a 17% reduction in RA risk.

Conclusions

Rheumatoid arthritis (RA) is a systemic, autoimmune, inflammatory disease of unknown etiology, characterized as a progressive disease, leading to joint destruction, physical activity limitation, disability, premature death, and imposes a significant economic burden on patients, family members, and society.

Identification individuals with an increased risk of RA may allow for the implementation of preventive activities and early diagnosis in patients with symptoms of RA. Early diagnosis based on the new criteria for classification of RA provide opportunity for early treatment of RA to prevent its progressive course and complications.

This paper presents environmental and personal risk factors for development of rheumatoid arthritis. Key

risk factors like smoking, periodontal diseases, vitamin D deficiency, obesity, environmental factors, menstrual disorders or menopause were presented in table 1 with preventing activities like smoking cessation, systematic dental and gynecological care, treatment of vitamin D deficiency, body mass normalization, reducing exposure to environmental factors and education on diet, breast feeding and alcohol use. Other Risk factors for RA development are family history of RA, presence of RF or ACPA, low socioeconomic status.

Presented data are mainly based on the latest medical reports and could be helpful for primary health care doctors, specialists and other people involved in diseases prevention, treatment and promotion of health.

Table 1. Rheumatoid arthritis – preventive activities.

Risk factors for RA development	Activities for RA prevention
smoking	smoking cessation
periodontal diseases	systematic dental care
vitamin D deficiency	treatment of vitamin D deficiency
obesity	body mass normalization
environmental factors	reducing exposure
menstrual disorders, menopause	systematic gynecological care
diet, breast feeding, alcohol use, traffic pollution	education

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