Geographical factors in rheumatoid arthritis

"*[Rheumatoid arthritis] is universally distributed and there is no ethnic group who have been described without it. Nevertheless, there is prominent information related to an unequal distribution of this potentially disabling disease around the world.*"

KEYWORDS: epidemiology ▪ rheumatoid arthritis ▪ risk factors

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Rheumatoid arthritis (RA) is a systemic inflammatory chronic disease of unknown origin that mainly affects adult women and tends to be more prevalent in the oldest group of people [1]. Fascinating facts have been seen during its history and many hypotheses have been raised on when it appeared, how it affects human beings and some interesting epidemiological findings and trends [2]. It is universally distributed and there is no ethnic group who have been described without it. Nevertheless, there is prominent information related to an unequal distribution of this potentially disabling disease around the world.

Is there a real difference on prevalence of RA among regions & ethnic groups?

Discrepancies in epidemiologic data have to be seen with caution. Although a real difference can be responsible for such findings, alternative explanations have to be explored such as: the quality of information being gathered (e.g., different sources of information have been used in prevalence studies, those clinically confirmed by a rheumatologist are more credible); different classification criteria (e.g., historical comparisons without the same classification criteria do not have a direct extrapolation); the type of healthcare services available (e.g., if clinical charts are used, in countries with low healthcare coverage, RA could clearly be under represented); and the distribution of population being studied (e.g., countries with predominantly young people could have lower incidence and prevalence rates due to age distribution). Even when all these possible explanations have been considered, it is well accepted that RA frequency varies among different regions and ethnic groups.

The largest incidence and prevalence rates have been seen in some native North American groups such as the Pima and Yakima Indians in the USA [3,4] and native populations in Canada. The prevalence reported is between 2 and 5% [5]. Australian Aboriginals have one of the lowest prevalence of RA, while the Australian white population has one of the highest rates of RA, near 2% [6]. The accepted prevalence in Northern Europe and white people in the USA ranges from 0.5 to 1.1%, while this number is lower in southern Europe, 0.3–0.7% [7]. Recent studies conducted in Mexico using the same methodology have detected important regional variation in RA prevalence [8].

Are genes responsible for this difference?

Genetic factors have been described in many autoimmune diseases and RA is no exception. We know that the possibility of having RA increases when a family member has this or other autoimmune disease. The shared epitope (SE; RA-associated alleles share amino acid sequences between positions 70 and 74 of the DRB1 molecule) has been associated with the development of RA and it seems to be also associated with disease severity, identified with the use of prednisone, bone erosions and higher levels of disability [9]. This SE has many subtypes and their distribution seems to vary among ethnic groups. This could explain differences in RA prevalence and disease severity. A study carried out in Texas has shown important differences in RA clinical presentation related to different gene distribution [9].

The SE is not the only gene associated with RA. Another group of genes that has been consistently found to be associated with RA is PTPN22 [7,10], but *HLA-DRB1* is the gene most strongly associated to date, and the only genetic factor that is associated with RA in all populations studied [10]. There is an additive interaction between HLA-SE and PTPN22,

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which increases the susceptibility to RA [11]. Interesting findings have postulated that the number of copies of the SE is associated with seropositive disease, radiographic changes, the frequency of rheumatoid nodules and increased sedimentation rate [9]. This effect could vary among ethnic groups.

The possibility of having protective genes has also been an interesting research field. It seems that gene *CYP17* polymorphisms found in Chinese patients is associated with a decreased risk of having RA in this population [12]. It is clear that other genes could also be responsible for protective findings [13].

What about environmental factors?

Some important environmental factors have been described in carefully conducted epidemiologic studies. Generalizability of epidemiologic results is not an easy task. It could be assumed that if they are not equally distributed, they could be responsible for some of the described geographical variations in RA prevalence in the world.

Tobacco is one of the most consistent finding that has shown a very important association with RA. Causality principles applied to tobacco exposure and RA show relevant data. This association is also related to genetic factors. The increased risk of having RA associated with smoking is higher after ten pack-years, and remains high even after 20 years of smoking discontinuation [7].

Those subjects with SE and PTPN22 have an increased risk of having seropositive RA if exposed to tobacco. This is explained through increased citrullination induced by tobacco [10]. The possibility of having anti-cyclic citrullinated peptide antibodies was more than five-times higher among smokers with two copies of SE compared with nonsmokers without it [14].

As a society we should move forward in terms of public health recommendations. We could prevent many cases of RA by decreasing tobacco consumption. Relevant clinical information also supports the concept that by decreasing tobacco consumption, even patients with RA could have better therapeutic response to some commonly used medications [15].

Moderate alcohol consumption in patients with RA has been associated with a less aggressive disease. Some studies have found that RA patients with a mild-to-moderate alcohol consumption had fewer erosions compared with no or high alcohol consumers [16].

■ Area of residency

A striking factor described in many studies is that RA is more prevalent in urban areas when compared with rural areas. Pollutants have been postulated as responsible for these findings. One study identified that living near a road was related to an increased risk of having RA [17]. Relevant epidemiological information needs to be obtained to answer this question.

■ Infections

It has also been mentioned that subjects in rural areas could be more exposed to different sources of infections and it has been described that they could have some protective effects, such as one described with malaria [18]. One of the most recently studied and an interesting epidemiologic finding is that periodontal disease has been associated with a higher risk of having RA. The postulated mechanism is citrullination produced by gingival bacteria [19]. This has also been associated with genetic predisposition and opens possibilities for prevention.

■ Perinatal factors

Subjects with more pregnancies have an increased risk of having RA [20]. This risk also increases with history and duration of breast feeding [21].

■ Nutritional factors

Nutritional factors have been postulated for many years to explain some discrepancies found in RA frequency among ethnic groups. One of the studies performed in Norfolk, UK, suggested that high red meat intake and a low intake of vitamin C could be related with arthritis, not necessarily described as RA [22].

■ Socioeconomic factors

It is intriguing to know that even countries with high standards of living have reported that subjects with low socioeconomic levels have a higher risk of having RA [23,24]. Mechanisms described could be related to tobacco consumption, exposure to pollutants and insecticides [25].

■ Obesity

Many subjects with RA and disease activity lose weight and RA is a well known cause of malnutrition. An interesting epidemiologic finding shows that RA patients who are obese have a less aggressive disease [26,27]. Experimental data propose that adiponectin and other adipocytokines could be responsible for an inverse association of adiposity and radiographic damage in RA [27].

Can we prevent RA?

From epidemiologic information it seems clear that genetic factors that predispose to RA vary among ethnic groups. Healthy lifestyles with adequate standards of living could decrease environmental hazards that trigger RA. Once RA appears, an organized healthcare system is needed for an early diagnosis and adequate medical treatment.

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