Resource

What is the cause of rheumatoid arthritis? Non-genetic factors

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Introduction

It is seldom possible to say why a particular person has developed rheumatoid arthritis (RA) but, in

general terms, the pieces of the jigsaw are coming together.

It is clear that there is a tendency for RA to run in families. If there is a family member with RA, the risk of developing RA increases by three-fold to nine-fold. If one member of a pair of identical twins has RA, then the other member has a 15% chance of developing the disease. This is substantially higher than the risk in the general population, which is approximately 0.8%. Since identical twins have identical genes, this high degree of what is called ‘concordance’ points to a major genetic contribution to the cause of RA. In twin studies, it has been estimated that the genetic factors determine 50% to 60% of the risk of developing RA. The fact that the concordance is not 100% means that other non-genetic or “environmental” factors also play a part. We are using the term “environmental” in a somewhat broader way than is common in everyday language. We are referring to the environment in which the genes have influence, and so we might include, for example, psychological stress, other medical illnesses and factors in the external environment such as pollution.

There is no single gene which is the cause of RA. There have been major advances in the last 10 years in terms of understanding the genetic factors which predispose to RA. Many of these have come from whole-genome scans in large cohorts of people with RA. More than 100 genes have now been identified, and work is currently in progress to establish exactly what these genes do and how they interact with one another and environmental factors. Similarly, there is no single environmental factor which is sufficient, by itself, to cause RA. We can think of RA as being like a plant. Firstly it needs the soil in which to grow. The soil is equivalent to genetic factors. Then there are the seeds which have to be planted in the soil. The seeds are equivalent to the non-genetic risk factors. The richer the soil (i.e., the more genes associated with RA a person has), the fewer the quantity of seeds needed for a plant to grow. Thus, within families with several cases of RA, it is likely that there are many of the genes which are associated with RA and so environmental risk factors play a smaller part in triggering the disease than in so-called ‘sporadic’ cases of RA. Also, since genetic factors are present from birth, whereas environmental factors are encountered throughout life, people who develop RA early in life are more likely to have a high number of genetic risk factors than those who develop RA later in life.

The Course of Rheumatoid Arthritis

There are several stages during the development of RA. First, there are the genetic risk factors which are called susceptibility genes. Secondly, there are the environmental risk factors for RA. It is only these factors which can be thought of as truly contributing to the cause of RA. The next phase is where there may occur various abnormalities in different parts of the body, such as the synovium, the gut and the lymph nodes. Many people who develop joint inflammation after, for example, a viral infection, get better within a few weeks. In other people, the arthritis persists and develops into RA. Before developing clinical RA, there is often a period of symptoms related to inflammatory arthritis. After the onset of clinical RA, there is a chronic phase. In this stage, genetic or environmental factors (including treatment) may influence the severity of the disease. It is very important to distinguish in which phase any particular gene or environmental factor plays a part. Only then can we know what the likely outcome would be of removing or modifying this particular factor. For example, if eating plums were a risk factor for developing RA (it isn’t as far as we know!) but had no effect on the severity of the disease once RA had developed, then there would be no point in advising people who had RA to stop eating plums. There might, however, be some merit in advising the non-affected member of an identical twin pair to stop eating plums in order to try and prevent the development of RA.

In order to find risk factors for the development of RA, we need to study people as close as possible to the onset of their symptoms. If we continue to study these people as their arthritis either gets better or progresses, we can learn about the genetic and environmental influences on the course of RA.

Clues from History and Geography

A study of the history and geography of RA provides some intriguing clues with regards to the cause of the disease. Within Europe, there are no definite descriptions of RA before 1800. It is surprising that the typical hand deformities which often develop after many years of disease, particularly if it is untreated, do not appear in medical or ordinary literature, paintings, or skeletal remains. This suggests that RA may be a “modern disease”. By contrast, in North America, skeletons have been found dating back several thousand years which do show evidence of RA. To this day, the highest frequency of RA is found amongst Native American peoples. This suggests that RA may have originated in the ‘New World’ and been transported to the ‘Old World’. The first candidate that springs to mind are an infection. However, we must not forget that other items such as tobacco and the potato were also transported from the New World to the Old.

The occurrence of RA is not the same throughout the world. RA is rare in less developed and rural parts of the world. One large study in Nigeria failed to find a single case. RA is also rare in rural China and Indonesia. An intriguing pair of studies from South Africa found a low frequency of RA amongst members of an African tribal group in a rural area and similar rates to those found in Europeans amongst members of the same tribal group who had moved to live in the city. This led to a theory that RA might be related to an industrialised lifestyle. However, the same pattern was not found amongst the Chinese. Low frequencies of RA were found in Hong Kong, which is a highly industrialised society. Perhaps the African people changed their diet when they moved to the city whereas the Chinese people did not.

Environmental Risk Factors for the Development of RA

1. Hormonal factors

Throughout the world, RA is more common in women than in men. This suggests that hormonal factors may play a part in the development of the disease. Although recent studies have not shown that pregnancy and parity (i.e. the number of liveborn children a woman has delivered) protect women from developing RA, women with parity of two or more children were 2.8 times more likely to develop RA compared to women with no children. After onset, RA usually goes into remission during pregnancy, and it is also very unusual for the disease to begin during pregnancy. The progression of disease activity in women with RA who become pregnant after disease onset is less than for those who are not pregnant, but this is mainly in those women who are auto-antibody negative (i.e. negative in blood tests for autoantibodies associated with RA).

The oral contraceptive pill has probably played a major part in reducing the occurrence of RA in younger women in the developed world over the last fifty years. The incidence of RA in women who have ever taken the Pill is around half that of women who have never taken the Pill. It is not clear whether this protection will be lifelong. It is possible that the onset of RA has simply been delayed until after the menopause. Postmenopausal women have a two-fold increased risk of developing

autoantibody negative RA, but not autoantibody-positive RA, compared to premenopausal women. There is as yet no evidence that hormone replacement therapy has any effect on the development of RA or that the Pill has any effect on the course of RA in women who have already developed the disease.

2. Other Medical Conditions

There has always been a widely held belief that RA was likely to be caused by an infection. Many researchers have dedicated their lives to trying to identify that agent, without success. It seems clear now that no single germ causes all cases of RA. However, in a substantial proportion of cases, RA begins within a few weeks of an infection of some sort. It is not that the infection persists but that the immune response to the infection does not “switch off” as it should. RA is a consequence of that immune response. Rarely, immunisation (which mimics, in a controlled way, the development of infection) can act as a trigger for RA in some people. However, it is likely that these people would have developed RA if they had caught the natural infection from which the immunisation was protecting them. With respect to other medical conditions, there is some evidence that diabetes mellitus might be associated with RA. Adipokines, which are cytokines, are thought to play a role in both diabetes mellitus and in RA.

RA is more common in people who already have another auto-immune disease, probably because of the shared genetic background.

3. Personal Risk Factors for the Development of RA

A number of lifestyle factors have been investigated to gain a better understanding of which factors may be associated with developing RA. To date, most results are inconclusive, and some lifestyle factors are associated with developing RA in men, but not in women and vice versa. Smoking is the most well-established risk factor for RA. The risk of developing RA is substantially higher in smokers, and smoking is associated with the presence of autoantibodies. There is also a trend in the number of pack-years (the number of packs of cigarettes smoked daily multiplied by the?number of years smoking) and the risk of developing RA with a 26% increased risk for every 10 pack-years smoked in men. However, this trend is less clear in women.

There is also some evidence that smoking influences the course of RA. Smoking appears to have beneficial effects on the amount of pain and joint tenderness which people with RA experience, and this may be why people with RA find it difficult to stop smoking. However, people with RA who continue to smoke are more likely to develop what is called extra-articular disease (meaning that they occur outside of the joints), such as nodules, involvement of the lung or inflammation of the blood vessels. There is some evidence that alcohol consumption might help to prevent the development of RA, but the results are less conclusive than those for smoking. Since obese people have levels of certain hormones such as leptin which also increases specific inflammatory cytokines, it is thought that obesity is associated with the development of RA. Some studies indeed have found a positive association between higher body mass index (BMI) and the risk of RA, but others only found this association in those who develop seronegative RA.

When considering socioeconomic status, which includes factors such as income, education, occupation, there is some evidence that people from lower socioeconomic backgrounds are more

likely to develop RA. However, socioeconomic status is a broad concept, and other factors may partly explain this association (e.g. BMI, smoking).

There is some evidence that certain components of the diet may increase the risk of RA in susceptible individuals. Diets high in red meat and low in vitamin C and other components of brightly coloured fruit and vegetables appear to carry an enhanced risk of RA. Conversely, the so-called Mediterranean diet appears to be relatively protective.

Conclusion

In people with many of the genetic risk factors for RA, exposure to a single environmental risk factor may trigger RA. However, in the majority of people, these factors (and others which have not yet been identified) probably act cumulatively, slowly lowering the threshold for the development of RA.

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