RECENT ADVANCES IN KNOWLEDGE CONCERNING GENETIC FACTORS WHICH PREDISPOSE TO RHEUMATIC DISEASES

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Arthritis is a very common condition that is seen worldwide. We don't know for certain the magnitude of this problem in the Islamic world due to shortage of pertinent information. Just to give you an idea of its prevalence in the United States, the second most frequent presenting complaint of the patients at physicians' offices pertains to the musculoskeletal system. Arthritis strikes in one out of three families and there are 31.6 million Americans with arthritis out of a total population of 211 million, 5.4 million of them are disabled by it. Osteoarthritis, also called degenerative joint disease, is the commonest type of arthritis, present in 7.5% of the population. Among inflammatory rheumatic diseases, rheumatoid arthritis is present in 3% and recent data indicate that ankylosing spondylitis may be present in more than 1% of the population.

The frequency of most types of arthritis changes markedly as a person passes from one decade of life to another, thus, every other person over the age of 65 years has arthritis. In addition, there are differences between males and females in the prevalence of arthritis, e.g., rheumatoid arthritis is more common in middle aged females, while ankylosing spondylitis is more common in young males. Hereditary factors have long been suspected as playing a part in susceptibility to arthritis and recent advances in immunogenetics have caused a renewed interest in this subject.

I would like to limit my discussion to some recent advances in our knowledge concerning genetic factors which predispose to rheumatoid arthritis and ankylosing spondylitis, two of the most common inflammatory rheumatic diseases. It has been found in the last five years that these two diseases occur more frequently in individuals who are born with certain types of genes on their 6th chromosome at an area called the major histocompatibility comples (MHC). The products of these genes are glycoprotein molecules expressed on cell membranes and are called human leukocyte antigens (HLA) because they were originally discovered on leukocytes. One of the HLA antigens, called HLLA-B27, is extremely interesting from both a clinical and research point of view. Approximately 8% of the general population are born with HLA-B27. Among patients with ankylosing spondylitis 94% are found to possess HLA-B27. This means that individuals born with HLA-B27 carry a much greater risk of developing ankylosing spondylitis than those who do not possess this antigen. HLA-B27 now serves as a genetic marker for ankylosing spondylitis and is being used as a useful diagnostic test, and also in epidemiological studies of this disease. Since ankylosing spondylitis can sometimes occur in individuals who lack HLA-B27, and only 20% of individuals born with HLA-B27 ever get this disease, additional factors, genetic and/or environmental, must be involved in its pathogenesis. Studies are currently in progress to find the specific disease susceptibility gene or genes which lead to ankylosing spondylitis and which are very closely associated with HLA-B27 gene.

There is ample evidence that immunologic factors play an important role in the pathogenesis of rheumatoid arthritis but the etiology of this disease is still unknown. Genetic predisposition to rheumatoid arthritis had long been suspected because of some reports of familial aggregation of rheumatoid arthritis, but the evidence was not convincing. Recently, a strong correlation of rheumatoid arthritis with an HLA antigen called HLA-Dw4 has been demonstrated. This observation, together with epidemiological evidence signify a genetic susceptibility to rheumatoid arthritis. HLA-Dw4 has been found in 54% of patients and only 16% of normal controls. This indicates that a person born with HLA-Dw4 has 6 times greater risk of developing rheumatoid arthritis than the rest of the 84% population that lacks HLA-Dw4.

Although the importance of genetic factors that predispose to ankylosing spondylitis and rheumatoid

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arthritis is now well established, we still don't know the events responsible for initiation of these chronic, potentially crippling and relatively common arthritic diseases. A genetically determined host response to some environmental agent or agents seems to be the most likely basis for pathogenesis of these diseases. Reiter's syndrome, a disease that has some clinical similarities with ankylosing spondylitis, appears to result from a reaction to non-specific urethritis or Shigella dysentery, although no infective agent has been firmly established as the cause of this disease. A similar "reactive" arthritis has also been noted after enteric infections with certain gramnegative bacteria such as Salmonella and Yersinia. Therefore, Reiter's syndrome (following urethritis or dysentery), "reactive" arthritis (following Salmonella and Yersinia enteritis), and possibly ankylosing spondylitis and rheumatoid arthritis (where no triggering factor is yet evident), all represent abnormal immune responses to infections in individuals who are genetically susceptible. This disease susceptibility is strongly associated with the gene for HLA-B27 in the above mentioned diseases except rheumatoid arthritis for which the susceptibility is associated with the gene for HLA-Dw4.

RECOMMENDED READING

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"The best proof of a man is not what he says but what he does."

Al-Tabib

"Behind every great deed there is a great sensitivity and a great thought."

Al-Tabib