Rheumatoid Arthritis: An Overview

Introduction

The first time I ever saw my grandmother in person during a family trip to China, I was shocked into silence. Her fingers were deformed, all of the joints curved the wrong way. She had to use a cane to walk, and when she did she appeared to be perpetually hunched over and moved fairly slowly and unsteadily. She was missing most of her teeth, and her jaw was strangely shaped. When I came back to the States, however, the image that stuck with me the most was that of the shape of her fingers, and their distinct lack of the natural curvature that I had noticed on my own hands. Why, my tactlessly curious nine-year-old self asked my mother, did Grandma look like that? My mom explained to me that Grandma had been living with a disease called rheumatoid arthritis that gave her deformed joints. As I grew older, she explained in more depth, telling me that the arthritis ate away at the cartilage between the bones in strange ways, resulting in the visible deformity. I have developed an interest in the disease, its diagnosis, and treatment methods, and have recently come to wonder whether it is at least in part genetically inherited.

Characterizing Rheumatoid Arthritis

Rheumatoid arthritis is a chronic systemic disease with various forms, including juvenile onset rheumatoid arthritis. It affects more women than men,

and the average age of onset is between 40 and 60. The disease is known to have autoimmune characteristics, and the genetic component is still under investigation as it is quite complex.

One of the main symptoms of rheumatoid arthritis is joint pain and stiffness. This is due to inflammation of the synovium, the membranous lining surrounding the body's joints, via immune system attack. The swelling and thickening of the synovium weaken and stretch the tendons and ligaments, forcing the joint to lose its shape and misalign. In severe cases, the deformed joint may invade and eventually destroy the surrounding layers of cartilage and bone. Other symptoms of rheumatoid arthritis include fever, puffy hands, fatigue, loss of appetite, and hard bumps just under the skin near joints, which are also known as rheumatoid nodules.

Rheumatoid arthritis has been linked to celiac disease. It is also linked to heart and lung problems as well as deformities of the joints, such as in the hands and feet, and bone erosion. Lung problems related to rheumatoid arthritis may be detected before the onset of joint problems. These include inflammation of the lining of the lung, also known as pleurisy; shortness of breath due to fluid accumulation from pleurisy, also known as pleural effusion; painful breathing; chronic dry cough; noncancerous rheumatoid nodules in the lungs, which if ruptured can cause a collapsed lung; and scarring of the lungs. Several eye problems have also been linked to rheumatoid arthritis. These include dry eyes, which can be a symptom of Sjogren's syndrome, a related

disease in which the body's lymphocytes destroy its own salivary and lacrimal glands; inflammation of the interior of the eye, or uveitis; inflammation of the eye's outer membranes, or episcleritis; scleritis, which causes severe eye pain and may cause the white of the eye to appear a deep violet color; glaucoma, which can result in blindness; and cataracts, which may also result in blindness.

Other possible complications include osteoporosis, carpal tunnel syndrome, and hardening or blockage of arteries. Smoking may increase the risk of rheumatoid arthritis.

Genomics of Rheumatoid Arthritis

Several genome-wide association studies have been done on patients with rheumatoid arthritis. Many of them have found that single nucleotide polymorphisms, or SNPs, in the HLA-DRA, HLA-DQA1, and HLA-DRB1 genes are correlated to a significantly higher number of patients with rheumatoid arthritis. The average odds ratio for each of these genes as determined by viewing a sample of recent genome-wide association studies is between 2.00 and 2.50. This indicates that individuals with single nucleotide differences in any one of these genes is more than twice as likely to be afflicted with rheumatoid arthritis as individuals without the particular polymorphisms.

The strong positive correlation between these three genes and the incidence of rheumatoid arthritis may provide further evidence that rheumatoid arthritis is indeed an autoimmune disease, as HLA-DRA, HLA-DQA1, and HLA-

DRB1 are genes that code for major histocompatibility complexes in humans. Major histocompatibility complexes, or MHCs, are proteins that enable cells to recognize other body cells as "self." It is logical to conclude that changes in MHC genes might cause defects in cellular self-recognition, which might in turn cause the onset of an autoimmune response. Of the three, HLA-DRB1 (chromosome 6q23) polymorphisms show the strongest correlation to increased incidence of rheumatoid arthritis. HLA-DQA1 is more strongly linked to celiac disease, which may begin to provide an explanation for the observed linkages between concurrent affliction of celiac disease and rheumatoid arthritis in patients.

Evidence suggests that polymorphisms in several other genes may also be associated with susceptibility to rheumatoid arthritis, including but not limited to SLC22A4, PTPN8, MHC2TA, IRF5, and NFKBIL1.

Rheumatoid arthritis is not known to differentially affect racial or ethnic subpopulations, although genome-wide association studies have been concentrated on Caucasians and East Asians.

Inheritance of Rheumatoid Arthritis

Rheumatoid arthritis is not known to be exclusively familial. It should come as no surprise that it is difficult to pinpoint the inheritance and heredity of rheumatoid arthritis despite researchers' suspicions of a MHC- or HLA-related susceptibility locus, because the genetic component of the disease is known to

be complex and has not yet been fully investigated. In addition, the environmental factors affecting rheumatoid arthritis need to be taken into account when investigating the disease and its patients, introducing many additional variables that complicate studies of inheritance.

Diagnosis of Rheumatoid Arthritis

Currently, it is difficult to definitively diagnose rheumatoid arthritis in its early stages due to the fact that the symptoms may be mistaken for those of a number of other conditions. During normal checkups, doctors may check joints for swelling, redness, and warmth. Doctors may also check for reflexes to ensure that joints are moving and working properly.

If doctors suspect that a patient might have rheumatoid arthritis, blood tests may be performed on the patient to test for elevated erythrocyte sedimentation rates, or ESR, which indicate an inflammation in the body. Blood tests may also seek information about rheumatoid factors and antibodies.

If a patient is already known to have rheumatoid arthritis, doctors may recommend X-rays so that the progression of the disease in the joints may be tracked over time.

New uses of magnetic resonance imaging, or MRI, are being developed to test for rheumatoid arthritis in patients. It was found that certain types of MRI can detect alterations in saturated fat signals, antibody levels, and bone erosion in patients. However, the study was performed on patients who were already

known to have non-erosive rheumatoid arthritis, which provokes the additional question of how to detect rheumatoid arthritis using MRI without prior knowledge of patient affliction.

Treatments for Rheumatoid Arthritis

At the time of writing, there is not much that can be done to actively fight rheumatoid arthritis. The most common method of "treatment" is focused on pain relief. Patients may be prescribed pain relievers such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, ketoprofen, and naproxen to reduce pain and swelling, respectively. Immunosuppressants such as azathioprine, cyclosporine, and cyclophosphamide can also be used to control the body's autoimmune response; however, using these drugs increases the risk of infection via external sources due to the suppression of the body's immune system. Steroidal medicines such as prednisone may also be used to reduce pain and swelling and slow joint damage, but only during the early stages of treatment, as prolonged use may decrease effectiveness while increasing severity and occurrence of serious side effects such as cataracts and bone thinning. Disease-modifying anti-rheumatic drugs, or DMARDs, can slow the progression of the disease and save other tissues from permanent damage. These include methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, and minocycline, and have severe side effects including liver damage, bone marrow suppression, and severe lung infections. DMARDs work slowly and often require

blood tests to confirm safety of patient usage. These drugs cannot be taken while pregnant. Currently, clinical trials are being conducted on several other DMARDs to determine their safety and efficacy.

For the most severe cases of rheumatoid arthritis and associated pain that cannot be treated effectively with drugs, surgery remains as an option. Joint replacements can greatly ease pain and correct deformities caused by the arthritis. Other procedures that may be performed include tendon repair around affected joints and joint fusion, which may stabilize and realign joints and serve as an alternative when joint replacement is not a viable option. It is important to remember that all surgical procedures carry risks of bleeding, infection, and pain.

Often, when treating lung problems related to rheumatoid arthritis, fluid removal procedures are necessary to clear the lungs and facilitate healthier breathing. Medication to suppress the immune system may also be prescribed.

Patients with rheumatoid arthritis may control the pain related to their disease by exercising gently, especially in water, although it is recommended to speak with a physician before beginning any exercise regimen in order to avoid the risk of injury. Rheumatoid arthritis is more painful for those who are overweight due to additional bone and joint strain; thus, patients who are heavier are encouraged to lose weight in order to relieve some of the strain and thus alleviate joint pain to a certain extent. For some patients, applying heat to

muscles to relax muscles and applying cold to numb the pain may also aid in pain relief.

Conclusion/Future Work

My grandmother has been living with rheumatoid arthritis for almost half of her life – over 30 years. I have seen firsthand the pain and hardships that come with this disease, and hope wholeheartedly that doctors and researchers may discover not only the root causes or factors affecting rheumatoid arthritis onset, but also treatments that can truly fight rheumatoid arthritis by detecting and stopping the disease in its early stages. In fighting the battle against rheumatoid arthritis, it is important to remember that the disease has both environmental and genetic factors, and both of these must be accounted for in any potential treatment regimen. In the meantime, the best recourse for the afflicted lies in the form of painkillers and as much light exercise as possible without injuring swollen joints so that the tissue remains in use.

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