Psoriatic arthritis

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Abstract

Psoriatic arthritis is a chronic inflammatory joint disease associated with psoriasis and a seronegative rheumatoid factor. The psoriasis is most commonly associated with the skin and nails, but there is also a possibility that it could affect the cardiovascular system, bowels, or eyes. The pathogenesis of psoriatic arthritis is not fully known, but there is a strong genetic linkage in the heritability factor and susceptibility. The diagnosis of psoriatic arthritis is done in most part by using laboratory data, radiology scans, and the classification criteria for psoriatic arthritis (CASPAR). CASPAR classification has five categories that are scored one or two points based on the answers. In order to test positive, the patient must score three or more points and present with an inflammatory articular disease. Along with that psoriatic arthritis patients, will commonly have inflammatory lower back pain, dactylitis, enthesitis, few counts for swollen joint count and tender joint count. The anti- cyclic citrullinated peptide and rheumatoid factor should be negative, and there will be a normal to sometimes elevated erythrocyte sedimentation rate and c- reactive protein. There is currently no cure but some symptoms can be treated with nonsteroidal anti- inflammatory drugs, disease-modifying antirheumatic drugs, and biologic disease- modifying antirheumatic drugs.

Introduction

Psoriatic arthritis (PsA) is known as an inflammatory arthritis associated with psoriasis that is typically negative for rheumatoid factor, is of an unknown pathophysiology, and it is classified as a part of the spondyloarthritis family (Boehncke, W.H. et al., 2014; Cantini, F. et al., 2010; Caso, F. et al., 2014; Silvy, F. et al., 2015). Diagnosis of psoriatic arthritis can be very difficult since there is not one definitive test marker. Instead, diagnoses rely on many criteria including, laboratory testing, radiologic tests, and the classification criteria for psoriatic arthritis (CASPAR). While there is no cure for psoriatic arthritis, there are several methods of treatment to attempt managing the disease, depending on the severity. There are also many other diseases and problems that can occur when a person has psoriatic arthritis.

History

Psoriatic arthritis was first classified in 1973 by Moll and Wright. They defined psoriatic arthritis as "patients seronegative for rheumatoid factor with positive history of psoriasis, current skin or nail psoriasis and inflammatory joints of axial disease." There were originally five categories for psoriatic arthritis that were based mostly on the features of the person's PsA. These categories were distal interphalangeal arthritis, asymmetrical oligoarthritis, symmetrical polyarthritis, spondylitis, and arthritis mutilans. While these are not the current categories, they do share many of the same features. The new categories are oligoarticular peripheral disease, polyarticular peripheral disease, axial disease with peripheral arthritis, and axial disease without peripheral arthritis (Cantini, F. et al., 2010).

As of 2006, a new system has come about to help diagnose PsA. This system is known as CASPAR and has a very high sensitivity (91.4%) and specificity (98.7 %) (Cantini, F. et al., 2010; Boehncke, W.H. et al., 2014). CASPAR contains a list of symptoms and tests and the

patient receives a designated amount of points for each positive result. Points are given for evidence or history of psoriasis, psoriatic nail dystrophy, a negative rheumatoid factor, presence or history of dactylitis, and radiologic evidence of juxta-articular new bone formation. The more positive results the more likely they are to have PsA.

Epidemiology/Pathogenesis

The prevalence of psoriatic arthritis in the total population is 0.25%; however, there is a much higher prevalence of PsA with the psoriasis community. Approximately one in four people with psoriasis will end up developing psoriatic arthritis (Caso, F. et al., 2014). PsA is the most common in the western white populations than in any other race, but it is found in many others. The onset for PsA is usually around the ages 35-55, although it can occur at any age. The frequency of psoriatic arthritis in males and females is about the same. However, males are more likely to have the spondylitic psoriatic arthritis, and females usually more commonly have a pattern of psoriatic arthritis similar to that of rheumatoid.

The pathogenesis of psoriatic arthritis is a combination of genetic, immunological, and environmental factors. Several genetic and molecular techniques have been able to associate PsA with the major histocompatibility complex, and PsA phenotypes have been associated with several of the class 1 human leukocyte antigen (HLA) genes (Caso, F. et al., 2014). Different HLA genes have been found to be associated with different types of psoriatic arthritis. For instance, the HLA-B27 gene has been found in association with axial disease, and the genes HLA-B38 and 39 are associated with peripheral arthritis.

While the exact pathogenesis of PsA is a mystery, considerable progress in deciphering the pathogenesis has been determined. Some single nucleotide polymorphisms (SNPs) have been shown to be susceptibility to PsA. These SNPs specific for PsA have been seen in IL23A,

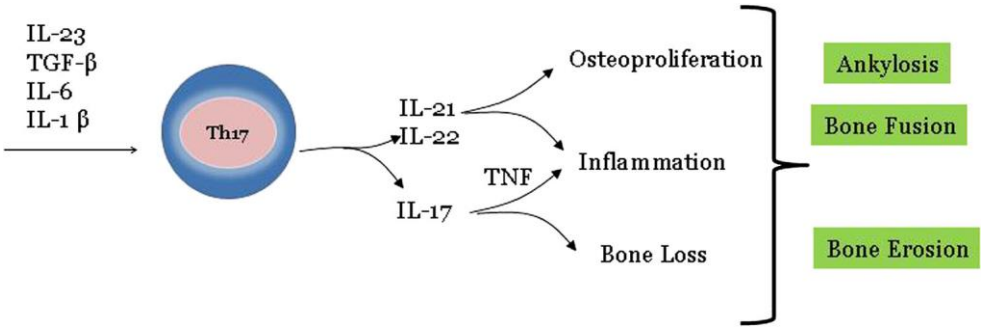
IL23R, and the gene TRAF3IP2, which is a downstream target for the IL-17 receptor. The TRAF3IP2 gene plays a central role in the innate immune response and responds primarily to pathogens, inflammatory signals, and stress. This gene interacts directly with TNF receptor associated factor proteins to activate nuclear factor kappa beta (NF-kappaB). NF-kappaB is a protein complex that helps control the transcription of DNA, cytokine production, and cell survival. If NF-kappaB is being regulated incorrectly it can lead to inflammatory and autoimmune diseases such as PsA.

When the immune system is activated the ending product is predominantly cytokines. While the complete understanding of cytokines role in PsA is still evolving, these cytokines that are produced play a vital role in the initiation and progression of the disease. A number of factors work in a complex pathway in order to determine the pathological events and tissue responses that are present in PsA. The pathway includes several T cell subpopulations, Th1, Th9, Th17, and Th22, along with their subsequent cytokines IFN-γ, TNF-α, IL-17, and IL-22. Also present in the pathway are chemokines, adhesion molecules, neuropeptides, and growth factors.

In several experiments using mice and humans it has been demonstrated that IL-23 activates Th17 cell which produce cytokines such as IL-17 and IL-22. These cytokines are responsible for serious adverse effects seen in PsA patients such as, development of psoriatic plaque, pannus formation in the joint, joint erosion, new bone formation, epidermal thickening, synovial inflammation, angiogenesis (formation of new blood vessels), and cell trafficking. IL-17 has many pathological roles in PsA that include, recruiting neutrophils to the epidermis of psoriatic lesion by increasing neutrophil specific chemokines, and induces TNF-α to be released from dendritic cells and macrophages. (Raychaudhuri, S. K., Saxena, A., Raychaudhuri, S. P., 2015)

In another study it was found that the synovial fluid of PsA patients was enriched with IL-17 that produced CD4+ effector memory T cells, and the most well recognized receptor for IL-17, IL-17RA. In a study in mice that were IL-17 deficient they had a lessened disease severity. The IL-17 deficiency results in impaired synovial expression which prevents cartilage destruction. Increased amounts of IL-17 that are usually presented in PsA patients will promote bone erosion by upregulating NF- kappaB ligand. IL-17 also activates TNF which will lead to excess inflammation and new bone formation. This is why PsA patients experience both Bone erosion and new bone growth and fusion. (Raychaudhuri, S. K., Saxena, A., Raychaudhuri, S. P., 2015)

Several environmental factors could affect PsA as well including, bacterial infections, smoking, stressful life events, recurrent lifting of heavy loads, and trauma injuries (Cantini, F. et al., 2010; Caso, F. et al., 2014).



Diagnosis

The process to receive a diagnosis of psoriatic arthritis is be a tasking endeavor that can take anywhere between a few months to years in order to confirm diagnosis. The diagnosis relies on several people and departments including the rheumatologist, radiology, and the laboratory. The rheumatologist makes the final decision whether to diagnose a person with psoriatic arthritis or not. There are several characteristic things they look for such as, specific characteristic inflammatory findings of the joints and spine, enthesis, the presence or history of psoriasis, and a

negative rheumatoid factor (Boehncke, W.H. et al., 2014). Using rheumatoid factor is a good way for the rheumatologist to distinguish rheumatoid arthritis from psoriatic arthritis. The majority of patients with PsA will not be positive for rheumatoid factor.

Rheumatoid factor is an antibody not normally present in a person that binds to the normal antibodies and is therefore termed an autoantibody. It is typically composed of IgM antibodies that react to the Fc portion of the IgG creating an immune complex. To test for rheumatoid factor blood is collected by venipuncture into tubes and brought to the lab for sampling. Then there will be a latex agglutination test performed with a positive control, a negative control, and the patient's sample. If there is agglutination that matches the positive control then the patient tests positive for rheumatoid factor. If there is no agglutination like the negative control then the patient tests negative ("Rheumatoid factor,"2014).

Rheumatoid factor is not the only test performed in the lab for psoriatic arthritis. Other commonly ordered tests are erythrocyte sedimentation rate, C- reactive protein, and fibrinogen. They are used to help gauge the amount of inflammation present in the body and are elevated in around 50% of the cases. Synovial fluid analysis of swollen joints is done to help rule out gouty arthritis.

A patient with psoriatic arthritis will not have urate crystals in their synovial fluid sample and a typical patient with gouty arthritis will. A psoriatic arthritis patient is more likely to have calcium pyrophosphate dihydrate crystals (CPPD) in there synovial fluid sample. The difference between monosodium urate crystals (MSU) and CPPD crystals is determined by using polarized light microscopy. When the CPPD aligned parallel with the compensator it will appear blue and have a positive birefringence. MSU crystals will appear yellow and have a negative birefringence. If the crystals are aligned parallel then the CPPD crystals will appear yellow and

the MSU crystals blue. Sometimes, there are also tests ordered for HLA. Most commonly ordered is HLA-B27 to test for psoriatic arthritis axial disease positivity, and HLA- B38 and HLA- B39 to test for psoriatic arthritis peripheral disease positivity.

When the rheumatologist has all this laboratory data in hand, along with the radiology scans, and the CASPAR system it makes it easier to cancel out all the things the patient doesn't have until the only thing left is psoriatic arthritis.

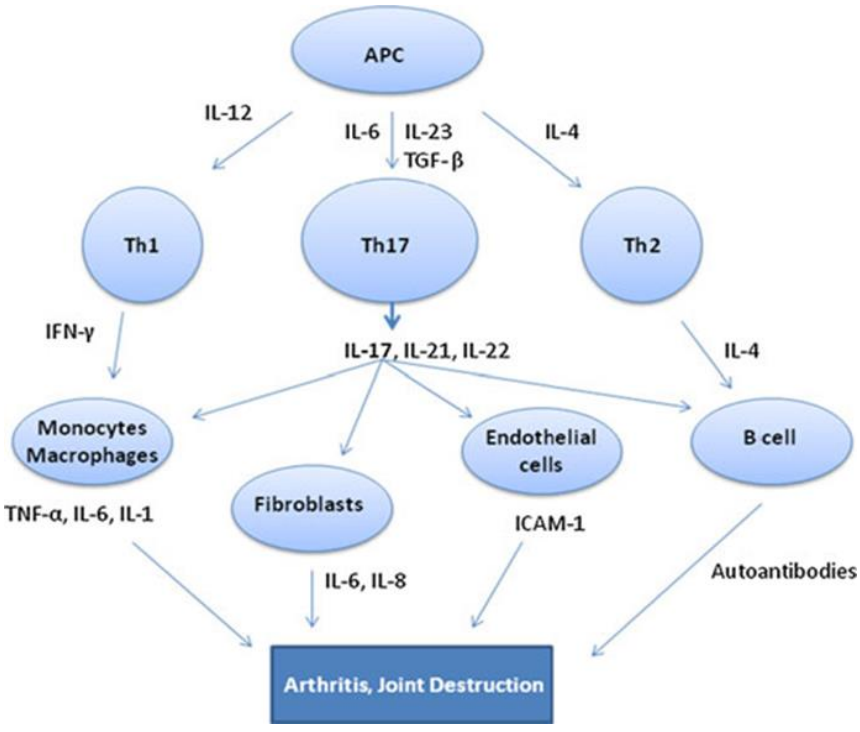
Treatment

After the diagnosis of psoriatic arthritis has been made treatment can begin. The majority of mild cases are treated with physical therapy and Nonsteroidal anti-inflammatory drugs (NSAIDs.) NSAIDs are medications, such as Aspirin, Excedrin, Ibuprofen, and Aleve. However, before patients begin treatment with NSAIDs they should be screened for potential medication toxicities. Patients should have a complete blood count, creatinine, and liver function test run before beginning treatment (Bergman M. J., 2014).

For patients with moderate to severe psoriatic arthritis, instead of the NSAIDs, they are treated with nonbiologic disease-modifying antirheumatic drugs (DMARDs). The DMARDs include medications such as Methotrexate and Leflunomide. Before being put on DMARDs the same tests should be run as with the NSAIDs, plus an additional screen for Hepatitis B and C. It is highly important to test for the core antibody for Hepatitis B in psoriatic arthritis patients that will be treated with DMARDs. This is due to the fact that many patients who have taken a DMARDs while being core antibody positive for Hepatitis B have had very bad reactions to their DMARDs (Bergman M. J., 2014).

The main thing psoriatic arthritis patients are treated with is biologic disease-modifying antirheumatic drugs. There are currently eight approved biologics in use to treat psoriatic

arthritis. Five of the biologics are tumor necrosis factor (TNF) inhibitors; Adalimumab (Humira), Etanercept (Enbrel), Golimumab (Simponi), Infliximab (Remicade) and, Certolizumab Pegol (Cimzia). Three of them are interleukin inhibitors. Ustekinumab (Stelara) inhibits IL-12/IL-23, while Secukinumab (Cosentyx) and Ixekizumab (Taltz) inhibit IL-17A (Caso, F. et al., 2014; Wait M., 2014). Each one of these drugs has their own screening process but overall the patient will probably be tested for Hepatitis B if they were not already for the DMARDs. Some doctors will order a complete blood count with a differential because the biologics are known to affect the bone marrow. Biologics with anti- TNF are also known to affect the liver function tests and can cause them to become elevated, therefore tests for liver functions are sometimes ordered. However, the tests for liver function and the complete blood count and differential are not required tests, only recommended (Bergman M. J., 2014).



Another medication called Apremilast (Otezla) works by blocking the activity of an enzyme called phosphodiesterase 4 (PDE4). PDE4 is found inside the inflammatory cells of the body, when you block the production it reduces inflammation. Apremilast (Otezla) is not a biologic it is an oral medication taken daily. (Wait M., 2014)

While none of the treatments can put a stop to or reverse the damage of psoriatic arthritis the NSAIDs, DMARDs, and biologics have proven to slow the progression of the disease and give the affected people a better quality of life.

Comorbidities

People with psoriatic arthritis are at a high risk for developing additional problems and diseases including, type II diabetes, cardiovascular disease, cerebrovascular disease, hypertension, hyperlipidemia, uveitis, and subsequently mortality. Uveitis is most commonly seen in patients with axial PsA and B27+ patients. The onset time is usually over one to two days and is categorized by having eye pain, redness, miosis, photophobia, and blurred vision. An eye examination will show inflammation of the anterior chamber and a presence of leukocyte precipitation. It is most commonly only seen in one eye but reoccurs often affecting both alternatingly, and is typically treated with topical therapy or corticosteroids.

In studies, even PsA patients without clinically evident cardiovascular disease have a significant increase of intima-media thickness and impairment of flow- mediated vasodilation. The vascular alterations causing the increased cardiovascular complications are believed to be due to pro-inflammatory T-helper type 1 cytokines, predominantly TNF-α (Caso, F. et al., 2014).

Another reason patients with psoriatic arthritis have an increased risk of cardiovascular disease and type II diabetes is due to the biologics they are put on to treat the PsA. In a recent study showed over a 24 week period the symptoms of the PsA were lower but there was a

significant increase in triglycerides, cholesterol, high-density lipoprotein, leptin, and body mass index.

There is direct relationship between increased inflammatory markers and cardiovascular problems. C- reactive protein (CRP) is an acute phase reactant produced by the liver that is stimulated by IL-6 and increases with inflammation. There is a direct correlation between a high CRP and coronary artery disease. Fibrinogen can also be used to show an increased risk of cardiovascular disease. Fibrinogen is a soluble glycoprotein that is produced by the liver and also has a direct correlation like CRP.

Psoriatic arthritis patients should have regular lab tests to help monitor the changes while they are on medications, and to asses there CRP and fibrinogen levels for risk factors. (Ehsani, A.H. et al., 2016).

Conclusion

Psoriatic arthritis is a very complex autoimmune disease that wasn't defined until 1972 and the diagnosis process has come a long way in a short amount of time, but still has much further to go. Luckily new testing is always on its way. Currently testing for anti-nuclear antibody patterns are in the works, as well as a test for a protein 14-3-3η (eta). The laboratory is a very vital portion of diagnosing PsA, without it the diagnosis and maintenance would be nearly impossible. The monitoring of lipid panels, liver functions, and inflammation tests are crucial information to the rheumatologist that help to determine on whether to keep a patient on a certain NSAIDs and biologic or not. While none of these medical options listed will give a person with psoriatic arthritis a perfect life they can help to manage the pain, reduce inflammation, and prevent further damage from occurring hopefully ensuring them a better quality of life.

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