THE ROLE OF THE LABORATORY IN THE DIFFERENTIAL DIAGNOSIS OF RHEUMATOID ARTHRITIS

Educational commentary is provided through our affiliation with the American Society for Clinical Pathology (ASCP). To obtain FREE CME/CMLE credits, click on Earn CE Credits under Continuing Education on the left side of the screen.

Learning Outcomes

On completion of this exercise, the participant should be able to

- compare the symptoms of the following diseases:
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Polymyalgia rheumatica
  - Ankylosing spondylitis
  - Lyme disease
  - Other infections, with agents such as HIV, Chlamydia, Campylobacter, Salmonella, Shigella, and Yersinia; and

- discuss the laboratory tests used to aid in the diagnostic differentiation of these diseases.

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disease. The immune system produces autoantibodies directed against the synovial membrane (lining) of the joint. Multiple joints are involved and inflammation occurs symmetrically on both sides of the body. The inflammation causes destruction of the cartilage and bone of the joints, often leading to deformity and disability. Organs such as the heart, lungs, and kidneys may also be affected. In the United States, approximately 1.5 million adults older than 18 years have RA, with the incidence in women 2 to 3 times that of men. The average age of onset is between the ages of 30 and 60.

Symptom review and physical examination are critical components of the diagnosis of RA. Hallmark symptoms of RA include fatigue, muscle aches and pains, joint pain with or without swelling, low-grade fever with no apparent cause, unusual weight gain or loss, and rashes. These symptoms are common in several other autoimmune and infectious diseases. Diseases that manifest symptoms similar to those of RA are systemic lupus erythematosus, ankylosing spondylitis, gout, Lyme disease, polymyalgia rheumatica, osteoarthritis, HIV infection, and others. It is important to distinguish among these diseases, particularly in RA, because early diagnosis (within 6 months of onset) and early initiation of appropriate treatment can reduce or prevent joint erosion and deformity. Because symptoms can vary greatly among individuals, diagnosis of patients with these diseases can be complicated, and often long periods of time, perhaps years, can elapse before an appropriate diagnosis is reached. Another factor contributing to the difficulty of diagnosis is that the symptoms may be acute (flare) and then ebb (remit) periodically.
THE ROLE OF THE LABORATORY IN THE DIFFERENTIAL DIAGNOSIS OF RHEUMATOID ARTHRITIS (cont.)

Autoimmune and Other Inflammatory Diseases that Mimic RA

Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect much of the body, including the joints, heart, lungs, skin, kidneys, blood cells, and brain. The age of onset is most commonly between 10 and 50. The disease is difficult to diagnose because its symptoms mimic several other disorders, including RA. In some patients with SLE, arthritis develops in the fingers, hands, wrists, and knees. Patients usually experience photosensitivity. The most distinctive feature of lupus is a butterfly-shaped rash that stretches across the nose and cheeks, but this rash occurs in only half of the cases.

Polymyalgia rheumatica (PMR) causes aching and stiffness in the shoulders, neck, lower back, and hips. It primarily affects individuals over the age of 50, with a mean age at onset of 70 years. As in most autoimmune diseases, women are at higher risk than men. Shoulder and hip joints are inflamed. Other symptoms are actually referred pain. Aching and stiffness is more severe in the morning or after long periods of inactivity. Although the disease may be very difficult to diagnose, in most cases, it responds quickly and dramatically to treatment with low-dose steroids. Differentiating PMR from elderly-onset RA can be difficult.

Ankylosing spondylitis (AS) is one of the almost 100 forms of arthritis. In AS, inflammation of the vertebrae can lead to the formation of new bone on the spine. The additional bone fuses the vertebrae and causes immobility. Curvature of the spine may develop and result in a forward-stooped posture. Involvement of the sacroiliac joint is the hallmark of the disease, but it may not be evident on x-rays for 7 to 10 years after onset. Although ankylosing spondylitis primarily affects the spine, it can cause stiffness in the joints of the shoulders, hips, ribs, heels, hands, and feet. The disease is more common in males, with an onset in early adulthood. There is a genetic correlation between HLA-B27 and AS. HLA-B27–positive populations are 20 times more likely to develop AS than HLA-B27–negative persons. It is thought that infection with Klebsiella triggers the disorder in HLA-B27–positive individuals. The risk for AS varies greatly with ethnicity. Ninety-five percent of Caucasians with AS are positive for HLA-B27, whereas only 50% of persons of African descent with AS are positive and 80% of persons of Mediterranean descent. Like RA, AS can present with joint stiffness and synovitis (inflammation of the lining of the joint). Joint stiffness is greatest in the morning or after a period of rest and lessens with activity, as does the stiffness in RA. Flares and remissions occur. Although 8% of Caucasians are positive for HLA-B27, 2% will develop AS.

Infectious Diseases that Mimic RA

Reactive arthritis is a painful form of inflammatory arthritis that occurs during and after infection with bacteria or viruses. As it fights the infection, the immune system produces inflammation in the joints of
some patients, causing the symptoms of arthritis. Symptoms include swollen, painful joints, usually in the knees, ankles, heels, toes, and/or fingers. Reactive arthritis is associated with infection with pathogens such as HIV, *Chlamydia*, *Campylobacter*, *Salmonella*, *Shigella*, and *Yersinia*.

Lyme disease is a bacterial disease caused by *Borrelia burgdorferi* and transmitted by the black-legged deer tick, *Ixodes scapularis*, in the northeastern and north central United States, and by the western black-legged tick, *Ixodes pacificus*, on the Pacific coast. The immature tick, or nymph, is usually responsible for transmission because it is small and difficult to detect on the body. The tick must remain attached for at least 36 hours to transmit the bacterium. Symptoms include fever, fatigue, headache, muscle and joint pain, swollen lymph nodes, and rash. The rash is called *erythema migrans* and resembles a bull's-eye. Up to 30% of infected persons do not have the rash, making the diagnosis more difficult.

**Laboratory Testing**

Diagnosis of RA relies on physical examination, patient history, radiologic findings, and laboratory testing. Laboratory testing includes assays for erythrocyte sedimentation rate or C-reactive protein to detect the presence of inflammation. Rheumatoid arthritis and all of the diseases that mimic it will cause elevated results on assays for inflammatory markers. The rheumatoid factor (RF) assay is positive in most, but not all, cases of RA. Rheumatoid factor is negative in approximately 20% of RA cases. The RF assay cannot be used to differentiate diseases that mimic RA, because the assay has high sensitivity but also a high rate of false-positives. Because the RF assay lacks specificity, positive RF results occur in patients with SLE, leukemia, various viral infections including infectious mononucleosis and HIV/AIDS, other autoimmune diseases, and diseases of the lung, liver, or kidney. Rheumatoid factor is also positive in 1% to 5% of individuals with no apparent disease. Therefore, the diagnostic utility of RF assays is limited and unreliable in differentiating rheumatic and infectious diseases. Rheumatoid factor testing is most useful when the results are negative and can help rule out RA; it is also negative in AS. High levels of RF indicate more severe or aggressive disease, and low or negative results indicate less aggressive disease. The anti-cyclic citrullinated peptide (anti-CCP) assay can also aid in RA diagnosis. The anti-CCP assay has similar sensitivity to that of RF, but its specificity is about 95%. Anti-CCP is often elevated years before symptoms appear, allowing early diagnosis and administration of therapy to minimize joint damage. A positive anti-CCP result is also used to differentiate elderly-onset rheumatoid arthritis from polymyalgia rheumatica.

Antinuclear antibody (ANA) testing is useful in differentiating other autoimmune diseases from RA. A positive ANA result with a homogeneous pattern at a titer of 640 or higher and a positive ds-DNA is highly indicative of SLE. Many autoimmune diseases will result in positive ANAs with speckled patterns. These
THE ROLE OF THE LABORATORY IN THE DIFFERENTIAL DIAGNOSIS OF RHEUMATOID ARTHRITIS (cont.)

include RA, mixed connective tissue disease, Sjögren syndrome, scleroderma, and sometimes SLE. These are differentiated by performing assays for extractable nuclear antigens including anti-RANA for RA, anti-Sm for SLE, anti-Scl 70 for scleroderma, and anti-SSA and anti-SSB for Sjögren syndrome. A positive ANA result is never used as the single diagnostic criterion for any of the autoimmune diseases. The ANA must be evaluated along with the patient’s symptoms, physical examination, and other medical testing before a diagnosis is proposed.

Infectious diseases are most commonly differentiated from RA by identification of the organism, bacterium or virus. This is accomplished by culture or serologic testing to detect antibodies produced against the organism. For most infectious diseases, serologic assays using agglutination or enzyme immunoassay are effective in identifying antibodies. In particular, the Centers for Disease Control and Prevention (CDC) recommends an enzyme immunoassay be performed to screen for Lyme disease. If the assay is positive or equivocal, it is followed by IgG and/or IgM Western blot. The Western blot differentiates Lyme disease from syphilis, leptospirosis, bacterial endocarditis, SLE, and other autoimmune diseases, which on enzyme immunoassay may cause a false-positive result for Lyme disease.

Conclusion

Many conditions produce symptoms similar to those of rheumatoid arthritis. It is important to diagnose each of these diseases as rapidly as possible so that appropriate therapy can be initiated. In RA, as in many of the other autoimmune diseases, early initiation of therapy can prevent much of the damage that may occur later in the disease. It is also important to properly diagnose bacterial infections so that appropriate antibiotics can be prescribed. The laboratory plays an important role in assisting physicians to arrive at the proper diagnoses for this myriad of diseases.

References


© ASCP 2015