EDUCATIONAL COMMENTARY – DIAGNOSING RHEUMATOID ARTHRITIS: THE ROLE OF ANTI-CCP

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LEARNING OBJECTIVES

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

- describe the role of anti-cyclic citrullinated peptide (anti-CCP) in the diagnosis of rheumatoid arthritis (RA).
- discuss the laboratory testing used in the diagnosis of RA.
- explain the formation of anti-CCP.
- describe the sensitivity of rheumatoid factor testing.
- list therapeutic agents used in the treatment of RA.

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that can affect many organs but most often affects the synovial membrane, the capsule that surrounds the joint. Diagnosis is difficult, because symptoms of RA overlap with those of several other diseases. Aching, stiffness, and swelling of joints are symptoms also common in systemic lupus erythematosus, psoriatic arthritis, gout, fibromyalgia, and infectious diseases. In many cases of RA, irreversible erosion of the joints occurs within the first year of the disease process. To prevent joint degeneration, early diagnosis and initiation of treatment is critical.

The American College of Rheumatology established criteria for the diagnosis of RA in 1987. Steps in the diagnostic process included a thorough patient history, physical examination of the joints, laboratory testing including rheumatoid factor assay and inflammatory assays, and radiologic studies. These criteria were based on clinical symptoms that had persisted for at least 6 weeks. In early disease, however, these clinical manifestations are often not present. As a result, under this system the diagnosis was likely to be delayed. In 2010, the ACR established new criteria for the classification of RA and recommended that patients who have at least one joint with definite swelling that is not the result of another disease be evaluated for RA. The new classification is based on a scoring system that includes the number of joints involved (small and/or large), results of serologic assays, and the duration of the symptoms. A score of 6/10 or more indicates RA. This system enables earlier diagnosis of RA in patients who do not display as many of the clinical symptoms as were necessary for diagnosis using the 1987 criteria. The new classification system was largely made possible by the development of an assay called anti-cyclic citrullinated peptide (anti-CCP), which is highly specific for RA.
For more than 50 years, the most common laboratory marker used in the diagnosis of RA has been rheumatoid factor (RF). Most assays detect immunoglobulin (Ig) M RF. The IgM RF assay is very sensitive but lacks specificity. Elevated RF is found in other conditions such as Sjögren syndrome, systemic lupus erythematosus, Epstein-Barr virus infection, endocarditis, leukemia, chronic hepatitis, and chronic viral diseases. Eighty percent of patients with RA have elevated concentrations of RF, but 70% of patients with Sjögren syndrome also have elevated RF levels. In 10% of healthy persons, especially elderly persons, RF results are positive. The lack of specificity of RF assays reduces the usefulness of the test in the diagnosis of RA. Although reference ranges for RF vary from procedure to procedure, most consider less than 30 U/mL or a titer of less than 1:80 as negative. Approximately 20% of patients who have RA are negative for RF. Higher levels are associated with more severe disease.

Patients with suspected RA are also tested for inflammatory markers. Erythrocyte sedimentation rate and C-reactive protein concentrations are elevated in inflammatory diseases. Tests for both of these are nonspecific for RA. Elevated results indicate inflammation but do not specify its cause. The fluctuation of C-reactive protein levels is more sensitive than changes in RF levels as an indicator of disease activity.

Citrullinated proteins in the synovia of the joints may be a major autoantigen initiating the local immune response in RA. In a common inflammatory process, citrullinated proteins are contained in dying cells, which are then cleared by the phagocytic cells. Conversely, in patients with RA, massive cell death occurs and the cells cannot be cleared. Intracellular citrullinated proteins are released from the dying cells. This activates the humoral immune system, which forms anti-CCP antibodies. The resulting immune complexes activate complement, perpetuating the inflammatory response in the joint.

All patients with RA do not produce antibodies to all of the citrullinated peptides. For this reason and to increase the sensitivity of the assay, the ELISA (enzyme-linked immunosorbent assay) second-generation procedure for anti-CCP (anti-CCP2) incorporates several epitopes of citrullinated peptides as its antigens. Anti-CCP assays are very specific for RA but have low sensitivity. That means that not all patients with RA are positive for anti-CCP, but almost all patients who are positive have the disease. There is a direct correlation between level of positivity and severity of disease. In patients who are positive, RA progresses more rapidly and causes more serious joint damage.

In the earlier ACR criteria for the diagnosis of RA, it was not diagnosed in patients with mild, nonspecific symptoms. The inclusion of the more disease-specific anti-CCP assay in the new criteria is the major enabler of earlier diagnosis and treatment of these patients. The anti-CCP assay has a specificity of 95% to 98% for differentiating RA from undifferentiated forms of arthritis. Elevated anti-CCP is a better indicator of erosive joint disease than RF level. The results of several studies indicate that anti-CCP may
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be present in some cases 12 to 14 years before the onset of RA.\textsuperscript{2-4} Because early initiation of aggressive therapy can prevent joint erosion, anti-CCP is useful not only in the diagnosis of RA but in its prognosis.

Therapy for RA ranges from exercise, occupational, and physical therapy to medications. Medications include nonsteroidal anti-inflammatory drugs such as naproxen or ibuprofen, steroids or immunosuppressants, disease-modifying antirheumatic drugs (DMARDs), and biologic response modifiers (BRMs). DMARDs and BRMs are the newest weapons in the arsenal of prescription medications for RA. DMARDs suppress the immune system, resulting in decreased pain and inflammation. If administered early in the disease, they can significantly slow the progression of joint damage. Because DMARDs often have serious adverse effects, it is important to properly diagnose RA before this therapy is initiated. The most common DMARDs are methotrexate, sulfasalazine, hydroxychloroquine and leflunomide. BRMs include interferons, interleukins, and tumor necrosis factor blockers. Biologic agents produced by living cells, BRMs are administered to restore the immune system's ability to fight off disease.

Anti-CCP has added an important tool for the diagnosis of RA. Its high specificity allows the physician to predict more severe, progressive disease in patients who are anti-CCP positive and to initiate treatment earlier. The result is a reduction in the degeneration of the joints and an improvement in the patient's future quality of life.

References


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