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## Rheumatoid Arthritis: Assessing Diagnostic Results in the Primary Care Setting

Announcer:

Welcome to CME on ReachMD. This activity, *Rheumatoid Arthritis: Assessing Diagnostic Results in the Primary Care Setting*, is brought to you by Prova Education and supported by an independent educational grant from Phadia, A Division of Thermo Fisher.

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Here's your host, Dr. Shira Johnson.

Dr. Johnson:

Rheumatoid arthritis, or RA, leads to inflammation that goes far beyond the joints, causing systemic manifestations like cardiovascular, pulmonary, psychological, and even skeletal disorders. Current guidelines focus on the importance of early recognition, diagnosis, and initiation of effective treatment

to prevent disease progression, but unfortunately, that doesn't always carry over into clinical practice. So, what can be done to combat these significant delays?

This is CME on ReachMD, and I'm Dr. Shira Johnson. Joining me today is Dr. David S. Pisetsky, Professor of Medicine and Immunology at Duke University Medical Center in Durham, North Carolina. We'll discuss how primary care providers can positively impact RA patient outcomes, such as through identifying and testing key inflammatory markers.

Dr. Pisetsky, thank you for joining me.

Dr. Pisetsky:

Well, thank you. I appreciate to be able to talk today again about rheumatoid arthritis, a very important inflammatory disease.

Dr. Johnson:

And I agree, it's a very important message to get out to our primary care providers that are listening to this, as well as other subspecialists. So, let's start by getting a better understanding of the problem. We know that many patients with RA present to the rheumatologist with advanced disease including: joint pain, swelling, and stiffness. But, what's the impact of this trend, and just how important is early recognition and diagnosis of RA?

Dr. Pisetsky:

Early recognition and diagnosis is very important. While rheumatoid arthritis is an inflammatory disease, it's also a disease that damages, and it damages the joints and can lead to deformity. Studies suggest that the earlier therapy is initiated and that therapy is guided by objective measures to do what we call treat-to-target, much better outcomes can be obtained, patients can have higher quality of life, less pain, and less progression to damage. The key is recognition of RA at the earliest stages to allow treatment to start.

Dr. Johnson:

Let's talk about why it's so important for primary care clinicians to have a high index of suspicion for RA and what diagnostic criteria they should be using.

Dr. Pisetsky:

Early recognition of rheumatoid arthritis is a challenge. There are 2 sources of delay. The first is from the patient. Patients may not know what the signs and symptoms of inflammatory arthritis are like, and because arthritis, in general, is common, patients themselves may not seek to have medical attention. The second delay is a lack of recognition of the signs and symptoms of early RA on the providers. Now, while RA is very common, individual providers may not see that many patients in their career who

present with early, what we call, synovitis, and they may not go down on the learning curve to recognize early arthritis. Unfortunately, teaching of musculoskeletal disease is not as robust and as active as we would like in medical schools and postgraduate training so that it may take a while before clinicians recognize the signs of rheumatoid arthritis.

The hallmark is what we call synovitis, which is inflammation of the joints. Now, inflammation is usually called red, hot, swollen and tender, but in early disease it can actually be quite subtle and take experience for its recognition. All that may be present is tenderness. The other problem here is that some of the other signs and symptoms of rheumatoid arthritis, such as fatigue, pain, depression, are very common in the population, so unless the connection is made to an arthritis, these other signs and symptoms may be not acted upon.

Dr. Johnson:

Let's talk about why it's so important for primary care clinicians to have a high index of suspicion for RA and what diagnostic criteria they should be using.

Dr. Pisetsky:

The key here is to understand what are the sort of cardinal signs and symptoms of RA, and these are emblematic and exemplified by the classification criteria. It's inflammation involving 3 or more joints, positive serology, which is either rheumatoid factor or antibodies to CCP, elevations of acute-phase reactants, which are either measured by C-reactive protein or the sed rate. It's also important to consider duration of symptoms. RA is a chronic disease, and symptoms must be present for at least 6 weeks before a diagnosis can be made. And then, it's also important to exclude other forms of inflammatory disease which can present similarly.

Dr. Johnson:

So then, it's important for a primary care clinician to refer the patient to a rheumatologist fairly early. Is that correct?

Dr. Pisetsky:

Antibody testing here provides important clues to the diagnosis. About 80% of patients with RA have a rheumatoid factor, and about a similar percent will have antibodies for citrullinated proteins, a test called anti-CCP. In the presence of inflammatory arthritis that's been persistent with a high sed rate, rheumatoid factors and anti-CCP provide good evidence for the possibility of RA, and that should lead to early and prompt referral.

Dr. Johnson:

So, you mentioned rheumatoid factor and CCP and other antibodies. Can you tell us a little bit more

about their specificity and sensitivity in diagnosing RA and what some of the studies have been in that regard?

Dr. Pisetsky:

Sure. Rheumatoid factors have been recognized for many years. They were sort of one of the first autoantibodies to be determined. A rheumatoid factor is an IgM antibody to IgG. While it probably has some physiological functions, it occurs commonly in many different inflammatory infectious diseases. It's a quite sensitive measure for RA, but it is not specific. So, if the pre-test probability for RA is high, a rheumatoid factor is quite informative. Antibodies to citrullinated proteins, so-called ACPAs, are recognized more recently. Citrulline is a post-translational modification of the amino acid arginine. The antibodies are directed to citrullinated proteins, but it's much more convenient to assay them with citrullinated peptides, and that's where the term anti-CCP comes from. Depending on the test, almost as many people with RA will have anti-CCP as rheumatoid factor, usually somewhat less, but this test is much more specific for RA than is rheumatoid factor. Both are useful depending on what tests are available from the laboratory. With people with arthritis who are anti-CCP positive or RF positive, a referral to a rheumatologist is indicated.

Now, it's important to note, however, that patients with rheumatoid arthritis may lack both of these antibodies, and about 10% to 20% of people with rheumatoid arthritis are what we call seronegative. So, laboratory testing does not exclude the diagnosis of rheumatoid arthritis; however, the combination of these tests gives much greater confidence that rheumatoid factor is there, and that allows clinicians to earlier therapy.

Dr. Johnson:

For those just joining us, this is CME on ReachMD. I'm Dr. Shira Johnson, and joining me today is Dr. David Pisetsky to review the roles of primary care providers in diagnosing RA earlier for patients.

Now, we just talked about measuring RF and ACPA and how that can lead to an earlier diagnosis. So, continuing on with this topic, what other diagnostic tests should a primary care provider consider?

Dr. Pisetsky:

Well, rheumatoid arthritis is a systemic inflammatory disease. Inflammation is manifest in terms of the laboratory, even in the complete blood count. Patients with RA can be anemic, their white counts can be elevated, their platelet counts can be elevated, and as I mentioned, their sedimentation and C-reactive proteins are also increased. And there are telltale signs of rheumatoid arthritis, especially involving the hands. Now, it's important to know that hands in rheumatoid arthritis can look normal by x-ray at the early stage, so that doesn't really provide evidence for it. However, if the signs of rheumatoid arthritis are there in terms of erosion, that test provides further evidence for the diagnosis. So, it's

usually a combination. I emphasize the importance of the physical exam. Arthritis in its early stages can frequently be difficult to detect. The joints are tender, but they may not be swollen, they may not be red, they may not be hot, so it's really important to get a sense of what early synovitis is like. It is a subtle disease that can be missed in its early form. And there are other tests that can be performed including an anti-nuclear antibody, or an ANA. This is a test that occurs positive in quite a few inflammatory diseases. Unfortunately, it's quite common in the otherwise healthy population, so for screening, it really has major limitations. So, for the primary care provider, I would focus on rheumatoid factor, anti-CCP, in conjunction with the physical exam, and then other laboratory findings of inflammation.

Dr. Johnson:

When the primary care doctors are interpreting the diagnostic tests, what should they pay attention to and keep in mind in terms of false-positives, false-negatives, and specificity?

Dr. Pisetsky:

The rheumatoid factor, I should say, shows up in other conditions, such as hepatitis, chronic infectious disease, endocarditis. It's really a manifestation of a very active immune system. So, people with rheumatoid factors frequently have other problems that need medical attention. Antibodies to CCP are different. They occur primarily in people with rheumatoid arthritis, but it's important to note that a person can be anti-CCP positive for many years before arthritis is present, and studies suggest they can be there 5 to 10 years before diagnosis really becomes clinically evident. Now, there's not really a reason to look for anti-CCP in otherwise healthy individuals or infected individuals; however, there are a few things that go along with an increased likelihood of RA, and that is somebody in the family with rheumatoid arthritis. So, sometimes this testing will be performed in people who are at risk for rheumatoid arthritis.

Anti-CCP is a quite specific test. Now, sometimes patients just present with what we will call arthralgia, which is joint pain, but they don't yet have signs of arthritis, which is synovitis. So, with just arthralgia, an anti-CCP really could be pointing towards arthritis even if the physical signs of RA are not yet present.

Now, while rheumatoid factor and anti-CCP are commonly done, the tests themselves are subject to some variability because of the different way they are constructed by manufacturers, the particular reagents that are used, and the levels of positivity that are considered to be significant. So, it's important for the laboratory to let the clinician know what values would be considered positive, what values would be considered negative for that particular test. Now, while a clinician may want to look in the literature about what the sensitivity and specificity are, this situation can be complicated because of

the number of different vendors or manufacturers providing these kits, so it's sometimes useful for the lab to tell the clinician, "This is the particular test we're using in our laboratory, so let's go over what would be positive, what would be negative, or what values would be intermediate." So, communication between the laboratory and the provider are very important in giving this key information about the range of tests that would be considered positive.

Dr. Johnson:

And lastly, Dr. Pisetsky, are there any other takeaways on RA that you'd like to share with our audience today?

Dr. Pisetsky:

One takeaway is just the importance of early recognition, because early recognition allows therapy to be started. The therapy that we have, especially when applied in what we call treat-to-target, which is an objective measure of disease activity based on the number of tender and swollen joints, an inflammatory marker and a patient report, has really shown impressive results with current agents. The process of erosion, which is joint damage, can basically be stopped, and progression to erosion also can be halted. So, early recognition can lead to very good results for many patients. The earlier therapy is started, the greater the benefit, and that should just lead to increased awareness on the part of primary care providers to the possibility of arthritis, recognizing that the diagnosis has to be substantiated by other testing, in particular laboratory findings.

Dr. Johnson:

Well, this has been a great look into how primary care providers can play a central role in the early diagnosis and management of rheumatoid arthritis. And I'd like to thank my guest for speaking with me and our ReachMD audience today. Dr. Pisetsky, it was great having you on the program.

Dr. Pisetsky:

Well, thank you very much. I appreciate being able to discuss this important condition.

Announcer

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