Elderly patients who complain of joint pain and stiffness usually have osteoarthritis (OA), but other forms of arthritis should also be considered. Rheumatoid arthritis (RA), for example, is an autoimmune disorder rather than a degenerative disorder that affects patients at all ages. Early diagnosis and treatment of RA can prevent or minimize irreversible joint damage. So it’s especially important to diagnose or rule out RA when a person presents with joint pain. In this newsletter, we’ll talk about a way to optimize diagnosis of early RA (symptoms <6 months duration).

**Diagnostic Approach**

The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) has created a classification scheme designed to identify early RA. Diagnosis begins with a history and physical. It’s important to note the number and size of joints involved and how long the patient has had symptoms. Inflammatory marker (C-reactive protein [CRP] and/or erythrocyte sedimentation rate [ESR]) test results, as well as rheumatoid factor (RF) and cyclic citrullinated peptide (CCP) antibody test results, should be obtained. This information is used in a scoring system designed to identify early-stage patients who are at high risk of persistent and/or erosive disease. Details of the scoring system and classification criteria can be found in the Figure and reference 3.

**Optimizing Early RA Diagnosis**

As discussed above, use of the ACR/EULAR classification criteria can help identify early RA. The serologic markers used (RF and CCP), however, are more sensitive in established RA than in early RA (Table). Combined use of RF and CCP does improve sensitivity, but it is still relatively low for early disease. Between 28% and 44% of early RA patients are seronegative, i.e., they test negative for both RF and CCP.4,5

**Table. Sensitivity and Specificity of RF, CCP, and 14-3-3 eta for RA**

<table>
<thead>
<tr>
<th>Markers</th>
<th>Early RA Sensitivity (%)</th>
<th>Established RA Sensitivity (%)</th>
<th>Specificitya</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF</td>
<td>57</td>
<td>84</td>
<td>85</td>
</tr>
<tr>
<td>CCP</td>
<td>59</td>
<td>79</td>
<td>99</td>
</tr>
<tr>
<td>14-3-3 eta</td>
<td>64</td>
<td>77</td>
<td>93</td>
</tr>
<tr>
<td>RF and CCPb</td>
<td>72</td>
<td>88</td>
<td>84</td>
</tr>
<tr>
<td>14-3-3 eta, RF, and CCPb</td>
<td>78</td>
<td>90</td>
<td>78</td>
</tr>
</tbody>
</table>

RA, rheumatoid arthritis; RF, rheumatoid factor; CCP, cyclic citrullinated peptide antibody.
a Comparison with healthy controls.
b Results considered positive for RA if any of the biomarkers are positive.
A novel biomarker, called 14-3-3\(\eta\) (eta), offers a way to further increase sensitivity for early disease. 14-3-3\(\eta\) is released from joints that are inflamed by RA. The 14-3-3\(\eta\) protein is slightly more sensitive than the other markers in early RA. It is more specific than RF but less specific than CCP (Table).\(^4\) When 14-3-3\(\eta\) is combined with RF and CCP, sensitivity for early RA diagnosis rises to nearly 80%. This improved sensitivity is due to the 14-3-3\(\eta\) test identifying 21% of seronegative patients with early RA.\(^6\)

**How the Laboratory Can Help**

Quest Diagnostics offers a selection of tests for ruling in, or ruling out, RA. These include tests for the general inflammatory markers (ESR, CRP) and the serologic markers (RF, CCP, and 14-3-3\(\eta\)). The serologic tests can be ordered separately or in a panel. Quest also offers tests that help differentiate RA from other conditions such as primary Sjögren syndrome, systemic sclerosis, gout, OA, and certain infections. Viral infections that may present with joint pain include hepatitis B and C, parvovirus B19, and rubella. Mosquito- and tick-borne infections such as chikungunya and Lyme disease may also cause joint pain.

**Additional Information**

Prevalence estimates for arthritis in the US population are\(^7-9\):
- 30.8 million people with osteoarthritis
- 8.3 million people with gout
- 1.5 million people with rheumatoid arthritis
- 740,000 to 2.0 million people with psoriatic arthritis

You can find more information at these Web sites:
- The Quest Diagnostics Test Center
  - Rheumatoid Arthritis Diagnostic Panel IdentRA® with 14-3-3 eta
test summary
  - Osteoarthritis and Rheumatoid Arthritis clinical focus
  - Autoimmune Rheumatic and Related Diseases clinical focus
- ACR/EULAR classification criteria for RA: ard.bmj.com/content/69/9/1580.full

**References**

**Spotlight on Health**

**Rheumatoid Arthritis**

Do you have joint pain or stiffness? Most people with these symptoms have osteoarthritis. But there are other kinds of arthritis, too. So before you start self-medicating with over-the-counter drugs for pain, see your doctor. It is important to find out if you actually have arthritis and, if you do, which type it is. If you have rheumatoid arthritis (RA), pain medication alone won't stop joint damage from happening. Other types of medicine might be able to, however. The earlier they are taken, the better the chance for preventing joint damage that lasts a lifetime.1

**What Is Rheumatoid Arthritis?**

RA is one of the many different forms of arthritis. It is an autoimmune disease in which the immune system mistakenly attacks the joints and harms them. This causes painful swelling and stiffness in the joints. Over time, the joints can become deformed and won't work properly. All of this makes it hard for a person with RA to do normal activities of daily living.

RA can harm other parts of the body, too. Sometimes the lungs are affected, leading to shortness of breath. People with RA are also more likely to develop heart disease. Some people with RA have a general feeling of fatigue, loss of appetite, and weight loss.

**How Can Doctors Tell If It’s Rheumatoid Arthritis?**

The first thing a doctor will do is find out about the symptoms. In RA, symptoms have a different pattern than those in other types of arthritis. For example, they often develop over the course of a few weeks or months instead of abruptly or over years. Symptoms may come and go instead of being there all the time. When there is morning stiffness, it can last more than an hour instead of less than an hour. Symptoms can be felt in joints throughout the body instead of in only 1 or 2 areas of the body. Other parts of the body could be affected too, not just the joints. These include blood vessels, heart, lungs, eyes, mouth, and skin.

Doctors can't always tell if it's RA based on symptoms alone. X-rays and other laboratory tests can help. For example, ESR and CRP are 2 lab tests that measure inflammation. Inflammation is common in RA and some other types of arthritis. But not all types of arthritis have inflammation. So these 2 tests help doctors tell 1 form of arthritis from another. The RF and CCP antibody tests can also help. Both of these antibodies are often present in RA, especially if a person has had it for a while. They are less common in other types of arthritis.

Sometimes doctors can't diagnose RA when the person first has symptoms. They have to wait until the disease progresses and more symptoms develop. This is a problem because treatment can't be started early, before the joints are damaged. New advances may be changing this, though.

**Symptoms of Rheumatoid Arthritis**

**In Early Stages**
- Pain in small joints of hands or wrists
- Stiffness in joints, especially in the morning

These symptoms can come and go.

**In Later Stages**
- Pain, swelling, and stiffness in 1 or more joints
- Morning muscle and joint stiffness
- Fatigue, loss of energy, lack of appetite
- Low-grade fever
- Joints red and warm to the touch
- Bumps under the skin
- Lung inflammation, which can cause shortness of breath
- Heart inflammation, which can cause chest pain
- Hoarseness caused by damage to a joint in the voice box
How Can Rheumatoid Arthritis Be Diagnosed Early?

One way is to use a scoring system developed by experts to help identify RA early.² The first step is to gather some information, including the number and size of joints that are swollen, painful, or stiff. Doctors will also find out how long these symptoms have been going on. Blood test results for ESR, CRP, and antibodies to RF and CCP are the final pieces of information gathered. The number and type of joints affected (large or small), the length of time of symptoms, and the blood test results are each given a point value. The higher the number of points, the more likely the disease is RA. A total of 6 or more points (out of 10) suggests that the person has RA.

Optimizing Early RA Diagnosis

Sometimes people have RA for a while before their body makes RF and CCP antibodies. So they might not have a positive test result in the early stages of RA. Using both of the tests helps, because maybe 1 of the 2 will be positive. Another way to improve early diagnosis is by adding a third test called 14-3-3η (eta).³ The 14-3-3η protein is released from joints that are affected by RA. Compared to the RF and CCP tests, it is positive a little more often in the early stages of RA. Using all 3 tests improves the chance of diagnosing RA in the early stages. The 3 tests together can identify close to 80% of people with early RA.

What Can You Do?

See your doctor as soon as you can if you have joint pain, stiffness, or swelling. Ask him or her to consider evaluating you for RA.

How Can The Laboratory Help?

The lab performs tests for inflammation (ESR and CRP). The lab also does tests for the RF and CCP antibodies and the 14-3-3η protein. These tests help the doctor diagnose RA in all stages.

The lab also does tests that can help differentiate RA from other types of arthritis. This can help the doctor know exactly what is causing a person's joint symptoms. Then the doctor can decide on the best treatment.

More Information

You can find more information at these Web sites:

- Arthritis Foundation⁶:
  www.arthritis.org/about-arthritis/understanding-arthritis/diagnosing-arthritis.php
- MedicineNet.com:
  www.medicinenet.com/rheumatoid_arthritis/article.htm
- WebMD:
  www.webmd.com/rheumatoid-arthritis/guide/default.htm

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The Most Common Types of Arthritis⁴-⁶

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis</td>
<td>30.8 million</td>
</tr>
<tr>
<td>Gout</td>
<td>8.3 million</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1.5 million</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>0.7 to 2 million</td>
</tr>
</tbody>
</table>

References