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Utility of common investigations for suspected inflammatory arthritis in adults

SUMMARY

Inflammatory arthritis may be the principal feature or one component of an inflammatory rheumatological disease. It is a clinical diagnosis, principally made based on the patient's history and examination.

Specific investigations, such as rheumatoid factor and human leucocyte antigen B27 gene, may support the diagnosis in the context of a suggestive clinical presentation, but a diagnosis cannot be made based on these tests alone because positive results may also be seen in healthy individuals.

To reduce the likelihood of false positive results, laboratory and radiological investigations should be tailored to the suspected diagnosis based on pretest probability. While musculoskeletal symptoms are a common presentation in general practice, specific features that increase suspicion of an inflammatory arthritis include prolonged morning stiffness (more than 1 hour) that is improved by exercise or movement.

A broad 'rheumatological panel' increases the likelihood of false positive results and should be avoided to prevent unnecessary further investigations and treatment, and unwarranted anxiety in both the patient and the doctor.

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Introduction

Musculoskeletal symptoms are very common in general practice, accounting for at least 1 in 5 presentations.[1] Many symptoms will be nonspecific (e.g. low back and neck pain), and some will be caused by osteoarthritis (e.g. knee pain), or a soft-tissue condition or injury (e.g. shoulder pain). These all increase with age. Inflammatory rheumatological diseases are a less common cause of musculoskeletal symptoms. These include conditions where the principal feature is inflammatory arthritis (e.g. rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis) and conditions where inflammatory arthritis may be one component of a multisystem presentation (e.g. systemic lupus erythematosus [SLE], systemic vasculitides).

The diagnosis of an inflammatory arthritis is primarily based on clinical assessment (i.e. history and examination findings), with results of laboratory and radiological investigations used to support such a diagnosis. Even relatively specific and useful tests, such as anti-cyclic citrullinated peptide (anti-CCP) antibodies for rheumatoid arthritis and the human leucocyte antigen B27 (HLA-B27) gene for axial spondyloarthritis, may be positive in healthy individuals. A diagnosis of an inflammatory arthritis cannot be made based on these tests without the appropriate clinical context.

However, in practice these investigations are often undertaken in patients without a suggestive clinical presentation (i.e. there is a low pretest probability of disease), increasing the likelihood of a false positive result and unnecessary further investigations and treatment.[2]

This article aims to provide guidance for general practitioners on the utility of common investigations when an inflammatory arthritis is suspected. The specific tests are listed in Table 1 and the indications for these tests are discussed below. The role of the commonly used inflammatory markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) is also covered. The article does not include clinical assessment of the relevant diseases.

Assessing pretest probability

Certain investigations are important to support or rule out the diagnosis of some inflammatory rheumatological diseases (see Table 1); however, healthy individuals can also have positive test results.

The pretest probability for a specific inflammatory rheumatological disease determines the utility, and therefore need, for a particular investigation in an individual patient. Pretest probability is the estimated probability that a patient has a disease before a test is done, based on the patient's clinical features, and the prevalence of the disease in the setting in

Table 1 Common associations of inflammatory rheumatological diseases where inflammatory arthritis may be a feature

Test	Associated inflammatory rheumatological diseases
rheumatoid factor	rheumatoid arthritis
anti-cyclic citrullinated peptide (anti-CCP) antibodies	rheumatoid arthritis
antinuclear antibodies (ANA)	systemic lupus erythematosus systemic sclerosis Sjögren syndrome rheumatoid arthritis dermatomyositis in adults
antibodies to extractable nuclear antigens (ENA)	limited systemic sclerosis (centromere staining pattern) systemic lupus erythematosus (homogenous or speckled staining pattern) diffuse systemic sclerosis (antibodies to Scl70) primary Sjögren syndrome (anti-Ro [SS-A] or anti-La [SS-B] antibodies) mixed connective tissue disease (antibodies to ribonucleoprotein [anti-RNP] – speckled staining pattern)
antibodies to double-stranded DNA (dsDNA)	systemic lupus erythematosus
human leucocyte antigen B27 (HLA-B27)	axial spondyloarthritis
antineutrophil cytoplasmic antibodies (ANCA)	ANCA-associated small-vessel vasculitides (eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, microscopic polyangiitis)

which the test is being used (i.e. the prevalence of rheumatological diseases in patients seen in general practice is lower than in patients seen in rheumatologist specialist practice).

Tests are most helpful in resolving diagnostic uncertainty in patients with an intermediate pretest probability. In these patients, a negative test result will lower the post-test probability of disease while a positive test result will increase it. If the pretest probability of disease is very low, testing is unlikely to be helpful as a positive result is likely to be a false positive. Similarly, if the pretest probability of disease is very high, testing may be unnecessary to confirm the diagnosis, but may be useful for determining likely prognosis and guiding treatment.

Box 1 lists features that increase suspicion of an inflammatory arthritis (i.e. raise the pretest probability). Other relevant factors, but of lesser importance, include a family history of inflammatory rheumatological disease (e.g. the various forms of spondyloarthritis share a genetic link with HLA-B27), ethnicity and sex (e.g. SLE is more common among Asian women). However, none of the above factors is specific and the patient's entire constellation of features needs to be considered. Symptoms such as fatigue and myalgia are very common in healthy individuals and are therefore less useful.

As with all investigations in medicine, before requesting an investigation, clinicians should be asking themselves: how will this test contribute to the patient's diagnosis and how will it influence management?

Box 1 Features that may increase suspicion of an inflammatory arthritis in patients presenting with musculoskeletal symptoms

- articular manifestations:
  - acute or subacute onset of symptoms
  - prolonged morning stiffness (more than one hour), improved by exercise or movement
  - features of synovitis such as joint effusion, boggy swelling, or warmth or tenderness of the joint
  - unexplained swelling of one or more fingers or toes suggestive of dactylitis (seen in seronegative arthritis)
  - typical distribution of affected joints (e.g. symmetrical, polyarticular, small joint involvement is most typical of rheumatoid arthritis)
- extra-articular manifestations (e.g. rashes, lung disease, uveitis)

Harms of overinvestigation

Requesting investigations in individuals with a low pretest probability of a particular inflammatory rheumatological disease increases the risk of false positive results and abnormal or equivocal results that are clinically irrelevant. Often these tests are done to provide reassurance, but they can have the opposite effect.

Harms associated with unnecessary investigations include:

- further unnecessary investigations
- unnecessary specialist referrals
- unwarranted anxiety in both the patient and the doctor
- misdiagnosis or overdiagnosis
- inappropriate treatment or overtreatment
- increased costs to the patient and Medicare.

Beware of the 'rheumatological panel'

It is not unusual for 'worried well' patients with nonspecific symptoms to be screened with a broad 'rheumatological panel' and then referred to a rheumatologist because one result is abnormal. Performing such a screen has a high risk of false positive results based on statistical principles. For example, if the reference range for an investigation is based on the central 95% interpercentile range in a group of healthy volunteers, then 5% of test results in the healthy population would be considered abnormal. This means, if 20 tests are ordered for an individual, an average of one test will have an abnormal result by chance.[3]

A broad 'rheumatological panel' is also unnecessary when the clinical presentation suggests a specific inflammatory rheumatological disease. For example, if a person is suspected of having rheumatoid arthritis, there is no need to perform an HLA-B27 test. In someone presenting with inflammatory back pain, there is no reason to perform tests for rheumatoid factor, anti-CCP antibodies or antineutrophil cytoplasmic antibodies (ANCA). In these circumstances, if the test result is positive, it is likely to be a false positive.

Erythrocyte sedimentation rate and C-reactive protein

The acute phase proteins C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are elevated during local and systemic events involving tissue inflammation, infection or injury. These markers can be helpful in discriminating between inflammatory and noninflammatory conditions, and to assess response to therapy or disease activity. However, they are nonspecific and, ESR in particular, may be elevated for reasons other than acute inflammation.[4]

ESR is a composite and indirect measure of the acute phase response. As such, ESR has low specificity, increases with age, is higher in females and in smokers, and may be elevated in patients with obesity. It takes 24 to 48 hours for the ESR to change in response to tissue insult.[5]

CRP is a direct measure of the acute phase response. It is generally accepted as the most accurate measure of the acute phase response as it is very low in healthy individuals and rises rapidly (within 6 hours) in response to inflammation.[5] It is not affected by age or sex.

In patients with suspected inflammatory arthritis, ESR and CRP can be useful for confirming inflammation (particularly ESR) and for monitoring disease activity (particularly CRP). However, there are times when, despite inflammation, neither CRP nor ESR are elevated. In some situations, ESR and CRP are discordant. For example, in patients with active SLE, ESR is more likely to be elevated than CRP, whereas in a patient with SLE who develops a bacterial infection, CRP is more likely to be elevated than ESR.

Specific blood tests

Rheumatoid factor and anti-cyclic citrullinated peptide antibodies

Rheumatoid arthritis is strongly suggested by clinical features, such as swelling in 5 or more joints (particularly in the hand and wrist), symmetry of the areas affected, symptoms present for longer than 6 weeks and early morning stiffness lasting longer than one hour. However, tests for the autoantibody rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies can help resolve diagnostic uncertainty in people with suspected rheumatoid arthritis.

The presence of rheumatoid factor has a relatively low sensitivity (approximately 70%) for rheumatoid arthritis and a specificity of approximately 80%.[6,7] Low titres of rheumatoid factor are not diagnostic (e.g. less than 30 international units/L) because they can be seen in healthy individuals and may also be present in a number of unrelated conditions, such as acute or chronic infections, interstitial lung disease or inflammatory connective tissue diseases.[6]

The presence of anti-CCP antibodies has a similar sensitivity to rheumatoid factor for rheumatoid arthritis, but is much more specific (specificity over 90%).[8] Anti-CCP antibodies may be present before the onset of symptoms.[9,10] High titres of anti-CCP antibodies are associated with a greater risk of erosive joint disease and a poorer prognosis.

A positive anti-CCP antibody result or a high-titre rheumatoid factor without suggestive clinical features does not confirm a diagnosis of rheumatoid arthritis and would not warrant treatment; however, the patient should be monitored clinically and cautioned to report symptoms of arthritis.

On the other hand, up to 30% of people with rheumatoid arthritis never develop rheumatoid factor or anti-CCP positivity (seronegative disease), so a diagnosis of rheumatoid arthritis can still be made based on clinical presentation alone.[11]

Once a diagnosis of rheumatoid arthritis has been made, regular monitoring of these antibodies is not required since a change in titre is not associated with a change in disease activity.

Antinuclear antibodies

Antinuclear antibodies (ANA) is a generic term for autoantibodies to various nuclear and other cellular elements. ANA testing is often used to screen for inflammatory connective tissue diseases, such as SLE; however, an ANA test may be positive in healthy individuals, though generally at lower titres.[12] For example, ANA is positive in more than 95% of people with SLE, but is also positive in 5% of healthy individuals at a titre cut-off of 1:160.[13,14] The incidence of false positive ANA results increases with age and in people with a family history of autoimmune disease.[12]

A positive ANA result may be seen in a broad spectrum of autoimmune disorders, including inflammatory bowel disease, autoimmune thyroid disease and rheumatoid arthritis. It is not specific to SLE or other inflammatory connective tissue diseases.

Key features that may warrant ANA testing include unexplained multisystem inflammatory disease, symmetrical joint pain with inflammatory features, photosensitive rash, Raynaud phenomenon (vasospasm of the digits) and sicca symptoms (dry mouth or dry eyes).[12] Nonspecific symptoms may also be present, but people whose only symptom is fatigue are unlikely to have a specific inflammatory connective tissue disease.

If the ANA result is positive in a patient with suggestive symptoms or signs of an inflammatory connective tissue disease, consider checking for antibodies to double-stranded DNA (dsDNA), which is more specific for SLE. Also consider checking antibodies to extractable nuclear antigens (ENAs), a panel of antibodies against different components of the cell nucleus. Positive ENA results can point strongly towards a specific diagnosis in the appropriate clinical context (e.g. antibodies to ribonucleoprotein [RNP] are seen in mixed connective tissue disease, antibodies to Scl70 are seen in diffuse systemic sclerosis, anti-Ro [SS-A] or anti-La [SS-B] antibodies are seen in primary Sjögren syndrome).[12]

The staining pattern of antibody binding is reported alongside the titre result and can also help point towards a specific diagnosis; for example, a homogenous or speckled pattern suggests SLE and a centromere staining pattern suggests limited systemic sclerosis. However, the dense fine speckled pattern (anti-DFS70 antibodies) is rarely associated with a systemic inflammatory disease and, in this instance, the patient can be reassured.

In the absence of highly suggestive symptoms or signs, a negative ANA result makes a diagnosis of SLE highly unlikely. In most cases, it is therefore inappropriate to perform further tests, such as an ENA panel or anti-dsDNA antibodies.[12] Some laboratories will restrict clinicians from requesting these tests without a positive ANA result.

Patients with a positive ANA result with an intermediate or higher titre (e.g. 1:640 or more) and mild nonspecific symptoms have a 10% risk of developing a definable inflammatory connective tissue disease and this usually occurs within 24 months.[15] These patients should be reassessed clinically after 12 months and repeat ANA testing only considered if there are new symptoms or signs that are more suggestive of a defined inflammatory connective tissue disease.[16]

ANA testing was highlighted in two of the recommendations by the Australian Rheumatology Association for the 'Choosing Wisely Australia' initiative, which aims to reduce inappropriate and unnecessary tests, treatments and procedures:[17]

- Recommendation number 2: Do not order ANA testing without symptoms and/or signs suggestive of a systemic rheumatic disease.
- Recommendation number 5: Do not order anti-dsDNA antibodies in ANA-negative patients unless clinical suspicion of SLE remains high.

Human leucocyte antigen B27

The human leucocyte antigen B27 (HLA-B27) gene is strongly associated with axial spondyloarthritis, an inflammatory arthropathy that affects the spine and typically presents in individuals younger than 45 years. The term axial spondyloarthritis incorporates both nonradiographic axial spondyloarthritis and radiographic axial spondyloarthritis (also known as ankylosing spondylitis). Nonradiographic axial spondyloarthritis is an earlier stage of disease where there is evidence of axial inflammation, but without definite changes on plain X-ray of the sacroiliac joints.

The HLA-B27 gene is found in 90 to 95% of people with axial spondyloarthritis, and a positive HLA-B27 result supports the diagnosis of a spondyloarthropathy in individuals with a suggestive clinical presentation (e.g. back pain at night with prolonged morning stiffness, symptoms present for more than 3 months in an individual who is younger than 45 years).[18] However, the HLA-B27 test has a low specificity for axial spondyloarthritis related to the prevalence of the HLA-B27 gene in the general population, and this varies with ethnic background. In Australia, the prevalence of the HLA-B27 gene is about 10% in healthy individuals, while the incidence of radiographic axial spondyloarthritis is approximately 0.5%.[16] This means that most people who have a positive HLA-B27 result do not develop radiographic axial spondyloarthritis.

The HLA-B27 gene is also found in people with other forms of spondyloarthritis (e.g. psoriatic arthritis, reactive arthritis), inflammatory bowel disease and isolated acute anterior uveitis. In people with these conditions the prevalence of HLA-B27 is between 30 and 50%.[19]

Antineutrophil cytoplasmic antibodies

While not all systemic vasculitides are associated with antineutrophil cytoplasmic antibodies (ANCA), a positive ANCA result is strongly associated with some systemic vasculitides (eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, microscopic polyangiitis). However, these diseases are rare and are rarely the cause of nonspecific musculoskeletal symptoms.

ANCA testing should not be used as a broad screen for inflammatory rheumatological diseases as the pretest probability is very low and false positives are likely. It should only be performed when there are specific features pointing towards a particular ANCA-associated vasculitis (e.g. active urinary sediment, unexplained vasculitic rash, unexplained systemic features such as weight loss and fever).

Radiology

Bony erosions are the radiological hallmark of rheumatoid arthritis. They are most commonly found in the small joints of the hands and feet, and are sometimes preceded by periarticular osteopenia. However, as erosions take months to develop, plain X-rays of the hands and feet are rarely of benefit in supporting a diagnosis of rheumatoid arthritis in individuals with early inflammatory arthritis symptoms. Furthermore, many individuals older than 50 years have some radiological changes of osteoarthritis reported on X-rays of their hands. The X-ray report may falsely reassure them that they have 'mild osteoarthritis' and miss the diagnosis of a superimposed inflammatory arthritis. In early inflammatory arthritis, when plain X-rays are likely to be normal, an ultrasound is more likely to demonstrate active tenosynovitis or synovitis and would be a more appropriate initial investigation. While magnetic resonance imaging (MRI) can demonstrate features of inflammation and joint damage, it is rarely indicated to support a diagnosis of peripheral inflammatory arthritis.

For people with suspected axial spondyloarthritis, plain X-ray of the sacroiliac joints is the imaging method of choice to assist in assessing the extent of joint and entheseal involvement and damage, as well as the rate of disease progression, but changes may not occur for some years. If the plain X-ray is normal, MRI may be an alternative imaging method for young people and those with a short symptom duration.

Findings on isotope bone scans are often nonspecific in differentiating musculoskeletal symptoms and rarely helpful in the investigation of a suspected inflammatory arthritis.

Conclusion

Diagnosis of an inflammatory arthritis is principally based on clinical assessment. Investigations where appropriate can be helpful in either supporting the clinical diagnosis or ruling out disease. Clinicians should consider the pretest probability of the patient having a specific diagnosis before ordering investigations and tailor their requests to the suspected disease.

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