Malaysian Family Physician 2009; Volume 4, Number 2&3
ISSN: 1985-207X (print), 1985-2274 (electronic)

Online version: http://www.e-mfp.org

Review: CME Article

COMMON LABORATORY TESTS FOR RHEUMATOLOGICAL DISORDERS: HOW DO THEY HELP THE DIAGNOSIS?

Esha Das Gupta *FRCP*, International Medical University, Seremban, Negeri Sembilan

Address for correspondence: Dr Esha Das Gupta, Associate Professor, Department of Medicine, International Medical University, Jalan Rasah, 70300 Seremban, Negeri Sembilan, Malaysia. Tel: 019-661 3975, Email: eshadgupta@yahoo.com

ABSTRACT
No screening test is ideal for detecting rheumatic diseases; diagnosis depends on appropriate history and thorough physical examination. Sometimes, laboratory investigations may be useful in confirming or ruling out rheumatic disease after a clinical diagnosis is considered. Once a rheumatic disease has been diagnosed, certain laboratory tests can help in assessing prognosis or determining the extent of the disease. Laboratory tests may also help the physician monitor certain rheumatic diseases, guide treatment or assess potential drug toxicity.
Das Gupta E. Common laboratory tests for rheumatological disorders: How do they help the diagnosis? Malaysian Family Physician. 2009;4(2&3):48-50

INTRODUCTION

Musculoskeletal complains are very common among the patients presenting to primary care.[1,2] Therefore it is important for the doctors to diagnose the condition and treat accordingly. Unfortunately many doctors did not receive adequate rheumatology training in their undergraduate years and are not well prepared to handle many of these conditions. Some doctors resort to laboratory investigations hoping that they will solve the diagnostic dilemma. But sometimes they may not be of great help. Let's look at some cases.

CASE 1

A 53 years old housewife presented with pain in her hands, wrists, and legs for last 6 months. She felt stiff when she tried to get up and could not do housework for the first half an hour. Examination revealed swelling of her PIP and DIP joints as well as swelling of both knee joints. There is no rash on the face or history of alopecia. Previous investigations, ordered by another GP, included a complete blood count and "arthritis screen" which showed an antinuclear antibody positive at a titre of 1:80 with a homogeneous pattern. Rheumatoid factor was positive at a titre of 1:20, and ESR of 32mm in first hour (normal range 14-20mm).

What would be your diagnosis? Would you consider her to suffer from rheumatoid arthritis, osteoarthritis or systemic lupus erythematosus?

ESR

ESR is a measure of the rate at which red blood cells settle through a column of liquid. In case 1, ESR is more than the normal range. ESR is sometimes helpful in distinguishing between inflammatory and non-inflammatory conditions. This test may be useful for monitoring patients with rheumatoid arthritis, polymyalgia rheumatica, etc.[3] However, this is not diagnostic and may rise in other conditions like infections, malignancy, anaemia and some other diseases. We must remember that ESR is directly proportional to age.[4] The rough calculation[4] for male is $\frac{age}{2}$ and for female is $\frac{age+10}{2}$. ESR rises with age and is of limited value in the elderly; an elevated ESR in an elderly patient should not prompt further investigation in the absence of clinical findings.

Rheumatoid factor

Rheumatoid factors (RF) are autoantibodies directed against the Fc portion of IgG. Rheumatoid factor is a misnomer; it may not point towards rheumatoid arthritis. Unfortunately, the measurement is not standardized in many laboratories. Rheumatoid factor is present in many people at very low levels, but higher levels are present in 5% to 10% of the population, and this percentage rises with age.[5] At diagnosis, only 60% of patients with rheumatoid arthritis test positive for rheumatoid factor.[6] However, they may be found in 75% to 80% of RA patients at some time during the course of their disease. High titre IgM RF is relatively specific for the diagnosis of RA in the context of a chronic polyarthritis. A titre above 1:80 may indicate the presence of rheumatoid arthritis; while a very high titre (e.g.,

Malaysian Family Physician 2009; Volume 4, Number 2&3
ISSN: 1985-207X (print), 1985-2274 (electronic)

Online version: http://www.e-mfp.org

1:512) may predict a more severe disease. This test should be done only if a patient shows evidence of polyarticular joint inflammation with sparing of DIP joints for a few weeks. Serial testing is not useful for patients with rheumatoid arthritis as this does not predict prognosis.

RF can occur in other connective tissue diseases, such as systemic lupus erythematosus (SLE) and primary Sjögren's syndrome. In addition, RF levels may be elevated in patients with certain infections, e.g. malaria, rubella, hepatitis C and following vaccinations.

Anti-cyclic citrullinated peptide (CCP) antibodies
ELISA assays based upon either filaggrin derived from human skin or synthetic citrullinated peptides, have high specificity and sensitivity for RA.[7] These antibodies are termed anti-cyclic citrullinated peptide (anti-CCP) antibodies. Among patients with early oligo- or polyarthritis, anti-CCP testing appears to be of predictive value in the IgM-RF negative subgroup. An ELISA assay that detects anti-CCP antibodies reportedly has a sensitivity and specificity of 47% to 76% and 90% to 96% for RA, respectively. Although anti-CCP antibody testing is more specific than RF[7], positive results can occur in other diseases. Positive results for CCP antibodies may occur in some patients with systemic lupus erythematosus or other autoimmune, connective tissue diseases and some non rheumatic diseases like chronic hepatitis C.

C-reactive protein
C-reactive protein is produced by the liver during periods of inflammation and is detectable in the blood serum of patients with various infectious or inflammatory diseases. The C-reactive protein is more reliable than the ESR and does not rise with anaemia.[8] Unlike the ESR, CRP can be measured using stored serum samples, is independent of the haemoglobin concentration.

So with this information, the first patient is unlikely to be suffering from SLE or rheumatoid arthritis. With the symptoms of swelling of PIP and DIP joints of the hands, she is most likely having osteoarthritis.

CASE 2

A 42 years old woman consulted you about generalized aches and pains in her limbs, low back and neck and intermittent headaches for last three years. She experienced fatigue and sleep disturbance. She has no morning stiffness, alopecia, photosensitivity, psoriasis, skin rash, dry eyes or dry mouth. She had not been able to work as a teacher for the last four months. Two years ago, her previous physician told her that, according to blood tests, she was having systemic lupus erythematosus. A physical examination reveals nothing remarkable except generalized tenderness. There was no evidence of joint inflammation. Previous investigations, ordered by another physician, included a complete blood count, a urinalysis and thyroid-stimulating hormone and creatinine levels; all were normal. This time, her test results were: ESR 36mm, rheumatoid factor positive and antinuclear antibody (ANA) positive (titre 1:16). Do you agree with her doctor's diagnosis?

Antinuclear antibody (ANA)
Antinuclear antibodies (ANA) are diverse, and some have specific disease associations. A positive ANA is one of the eleven criteria used in the diagnosis SLE.

The ANA test is positive in 98% of patients with SLE, 40%- to 70% of those with other connective tissue diseases; up to 20% with autoimmune thyroid and liver disease and in 5% of healthy adults.[9] The significance increases at a cut off titre of 1:160 or higher.[9] But a positive test does not by itself ensure a diagnosis of SLE. The ANA is of no value in monitoring disease activity and, thus, does not need to be repeated. A low-titre ANA is of no importance. Hence in a person with negative ANA the diagnosis of SLE is practically ruled out . It may be present in many normal individual. If the history and physical examination are unremarkable, no further investigation of a positive ANA is necessary.

Anti double-stranded DNA (anti dsDNA)
These antibodies are relatively specific (95%) for SLE, making them useful for diagnosis.[10] A negative test does not rule out the disease, however, because anti-dsDNA antibodies only occur in up to 60% of patients with SLE. Testing for anti-dsDNA may be useful in patients with a positive ANA test and clinical suspicion (i.e. skin and/or joint involvement) for systemic lupus erythematosus. Testing is not recommended in patients with a negative ANA test. This test should not be performed as a routine screening process for patients with aches and pains.

To make a preliminary diagnosis of a rheumatic disease, the doctor must take an extensive patient history and perform a thorough physical examination. No screening tests exist for arthritis; thus the "arthritis screen" of ordering a number of laboratory tests for patients with joint or muscle pain can lead to a false-positive result or can mislead the GP into thinking that there is no rheumatic disease.

Does the patient require more tests?
The patient has no clinical evidence of SLE. According to the history and examination, her symptoms of non-specific aches and pains, sleep disturbance and fatigue are soft tissue in nature. The low-titre positive ANA and rheumatoid factor are non-specific and do not require further investigation. None of these tests needed to be ordered. The patient can be reassured that she does not have SLE.

Malaysian Family Physician 2009; Volume 4, Number 2&3
ISSN: 1985-207X (print), 1985-2274 (electronic)

Online version: http://www.e-mfp.org

The above patient does not fit even the picture of rheumatoid arthritis either. She is suffering from fibromyalgia.

Other commonly used laboratory investigations

Complements C3 and C4

Decreased levels of complement arise from immune-complex disorders such as SLE and other selected forms of vasculitis. Complement testing is useless for screening of SLE but is often used to monitor disease activity in patients with SLE.[11]

Serum uric acid

Serum uric acid measurement is helpful in monitoring the extent of hyperuricemia in patients with gout. The prevalence of asymptomatic hyperuricemia among men is 5% to 8%, and fewer than 1 in 3 people with hyperuricemia will ever develop gout.[12] It is important to note that asymptomatic hyperuricemia does not confer a diagnosis of gout and need not be treated unless serum uric acid levels are persistently above 760 μmol/L (12.8 mg/dL) for men or 600 μmol/L (10.0 mg/dL) for women. At these levels there is an increased risk of renal complication.[13] Serum uric acid testing is often ordered for the patient with acute monoarthritis. Unfortunately, this will not be helpful in the diagnosis because of the high prevalence of asymptomatic hyperuricemia. A diagnosis of acute gout can only be made with certainty by joint aspiration to confirm the presence of urate crystals under polarized light.

Antibodies to extractable nuclear antigens (ENA)

Extractable nuclear antigens (ENAs) are specific antinuclear antibodies obtained from the blood. There are a large number of ENAs, but most are used for research purposes. Commercially available ENAs include anti-Ro, anti-La, anti-Smith, anti-RNP and in some labs, anti-Jo. A test for antibodies to ENAs (anti-ENA) should be ordered only if there is a suspected or known connective tissue disease and the ANA test is positive at a significant titre (i.e. 1:160 or higher).[14]

Antineutrophil cytoplasmic antibody test

Antineutrophil cytoplasmic antibodies (ANCAs) are autoantibodies to the cytoplasmic constituents of granulocytes. They are detected by indirect immunofluorescence on ethanol-fixed neutrophils and produce a characteristic cytoplasmic fluorescence (c-ANCA) or perinuclear fluorescence (p-ANCA). ANCAs characteristically occur in vasculitic syndromes.[15] A primary care physician will rarely need to order this test; it helps in the diagnosis and management of only a very small number of patients with relatively rare conditions and screening patients with non-specific symptoms results in many false-positive p-ANCA results.

Point to note is laboratory testing in rheumatology rarely "makes" a diagnosis. It has most value when used to support or refute a clinical impression It is important to be aware of false-positives and false-negatives. Still a detailed history and a thorough physical examination is the key to a correct diagnosis. Hence one should not blindly depend on the "arthritic screen" provided by commercial laboratories.

REFERENCES

1. Clarke A. The burden of rheumatic disease. *Medicine*. 2006;34(90):333-5
2. Taylor W, Smeets L, Hall J, *et al.* The burden of rheumatic disorders in general practice: consultation rates for rheumatic disease and the relationship to age, ethnicity, and small-area deprivation. *N Z Med J*. 2004;117(1203) U1098
3. Sox HC Jr, Liang MH. The erythrocyte sedimentation rate: guidelines for rational use. *Ann Intern Med*. 1986;104(4):515-23
4. Miller A, Green M, Robinson D. Simple rule for calculating normal erythrocyte sedimentation rate. *BMJ*. 1983;286(6361): 266
5. Chen P. Rheumatoid factor. *Rheum Dis Clin*. 1989;13:545
6. Lichtenstein MJ, Pincus T. Rheumatoid arthritis identified in population-based cross sectional studies: low prevalence of rheumatoid factor. *J Rheumatol*. 1991;18(7):989-93
7. Nishimura K, Sugiyama D, Kogata Y, *et al*. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med*. 2007;146(11):797-808
8. Kushner I. C-reactive protein in rheumatology. *Arthritis Rheum*. 1991;34(8):1065-8
9. Tan EM, Feltkamp TE, Smolen JS, *et al*. Range of antinuclear antibodies in "healthy" individuals. *Arthritis Rheum*. 1997; 40(9):1601-11
10. ter Borg EJ, Horst G, Hummel EJ, *et al*. Measurement of increases in anti-double-stranded DNA antibody levels as a predictor of disease exacerbation in systemic lupus erythematosus: a long-term, prospective study. *Arthritis Rheum*. 1990;33(5):634-43
11. Esdaile JM, Abrahamowicz M, Joseph L, *et al*. Laboratory tests as predictors of disease exacerbations in systemic lupus erythematosus: why some tests fail. *Arthritis Rheum*. 1996;39:370-8
12. Hall AP, Barry PE, Dawber TR, *et al.* Epidemiology of gout and hyperuricemia: a long-term population study. *Am J Med*. 1967;42(1):27-37
13. Pittman JR, Bross MH. Diagnosis and management of gout. *Am Fam Physician*. 1999;59(7):1799-806,1810
14. Love LA, Leff RL, Fraser DD, *et al*. A new approach to the classification of idiopathic inflammatory myopathy: myositis-specific autoantibodies define useful homogeneous patient groups. *Medicine (Baltimore)*. 1991;70(6):360-74
15. Niles JL. Value of tests for antineutrophil cytoplasmic autoantibodies in the diagnosis and treatment of vasculitis. *Curr Opin Rheumatol.* 1993;5(1):18-24