RHEUMATOLOGY IN PRIMARY CARE

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CHAPTER - 12

INVESTIGATIONS IN RHEUMATOLOGIC DISEASE

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A good history and detailed clinical examination of patient are extremely important for proper diagnosis of over 100 types of arthritis. Recognition of patterns of joint involvement (topography) as well as those of disease presentation and progression is essential for correct clinical diagnosis. A working diagnosis can usually be made on proper clinical examination of the patient. Laboratory tests, X-Rays and other investigations are ordered later for confirmation of diagnosis, ruling out other possible causes, estimating level of disease activity or monitoring drug toxicity. All investigations must be obtained from a reliable laboratory and the results should always be interpreted in view of clinical picture. Many tests are expensive and must not be used indiscriminately. Laboratory studies are useful in arthritis only if ordered in an appropriate clinical situation and interpreted accordingly (See Table 12.1 for list of preliminary investigations). Measurement errors, laboratory variations due to various factors and inherent limitations must always be borne in mind. A positive test in absence of appropriate clinical setting can generally be overlooked.

Table 12.1 Suggested preliminary investigations

1. Polyarthritis - Blood count, ESR, rheumatoid factor, X-ray of both hands with wrists (posteroanterior).
2. Osteoarthritis - X-ray individual affected joint only to assess degree of cartilage damage. X-ray of hands and wrists useful in suspected nodal or generalised OA.
3. Gout - Single most useful test is synovial fluid microscopic examination with polarized light for crystals. Urate, liver function tests and urea and electrolytes are usually needed in the assessment. X-ray of the affected region helpful in chronic cases.
4. Ankylosing spondylitis - Blood count, ESR/CRP, X-ray of pelvis. Please do not check HLA B27 - this may mislead. No isotope scans.
5. Lumbar or cervical spondylosis - The diagnosis should be based on history and clinical findings. Investigations for exclusion of other serious pathology.

ACPA and ANA are not 'diagnostic' or 'screening' tests. They should not be used to exclude a diagnosis of RA, SLE or other connective tissue diseases. Correct interpretation of results as applied to clinical condition of individual case is essential.

Commonly used laboratory investigations are discussed below:

Haemogram (Complete Blood Count - CBC)

This simple and inexpensive test gives valuable information about anaemia. Morphology of red cells and other observations give a clue to the cause of anaemia. Bone marrow suppression is a common adverse effect of some drugs such as methotrexate, leflunomide and azathioprine. Counts of white cells and platelets are also important in diseases like systemic lupus erythematosus (SLE) for diagnosis and follow up.

Erythrocyte sedimentation rate (ESR)

Liver produces acute phase reactants such as fibrinogen, haptoglobin, alpha-1-antitrypsin, C-reactive and other proteins in response to inflammation. This production is stimulated by Interleukin-1, an inflammatory cytokine. Normal age-adjusted upper limit of ESR is age/2 for males and (age+10)/2 for females. Westergreen method is more accurate for ESR levels of more than 50 mm/hr as it uses longer tube. Wintrobe method is more accurate for borderline elevations. Sample for ESR must be obtained in a fasting state and examined immediately. ESR is nonspecific for disease process. Aging, puberty, obesity and pregnancy elevate ESR. Anaemia, hypercholesterolemia and polycythemia also give higher readings. ESR can be markedly elevated in various infections, malignancies, paraproteinaemias and inflammatory rheumatologic diseases such as rheumatoid arthritis (RA) and SLE. Significant and persistent elevation of ESR in a case of arthritis indicates inflammatory process such as RA. It can also be used for monitoring efficacy of treatment in controlling disease activity. It must be noted that ESR remains elevated for longer time after inflammation subsides.

C-reactive protein (CRP)

CRP, a glycoprotein, is another acute phase reactant and. Though costlier than ESR, it is more specific marker of acute inflammation. It elevates within 4 hours of injury and peaks within 24-72 hours. Half life of CRP is about 18 hours and it disappears rapidly when the inflammation subsides. It can be estimated from a refrigerated sample. Estimation of CRP can also be used to monitor disease process. CRP is usually moderately elevated in inflammatory connective tissue disorders. Markedly elevated levels indicate acute bacterial infection, trauma and systemic vasculitis. Discrepancies between ESR and CRP can be found in SLE and other conditions wherein ESR is elevated whereas CRP remains normal.

Other markers of inflammation include anaemia of chronic disease (normocytic normochromic), leucocytosis, thrombocytosis, hypoalbuminimia and elevated alkaline phosphatase and ferritin levels. These are hardly ever required for diagnosis of inflammatory arthritis. Serum protein electrophoresis directly quantifies acute phase response and is most sensitive test for detecting inflammation.

Rheumatoid Factor

Rheumatoid factors are autoantibodies directed against Fc portion of IgG immunoglobulin. Development of rheumatoid factor (RF) is a mechanism to help removal of immune complexes from circulation. RF positivity is observed in many conditions such as hepatic and pulmonary diseases, infections (malaria, tuberculosis, Hepatitis C), sarcoidosis, neoplasia, Sjogren's syndrome and other rheumatologic conditions. This suggests that long term stimulation of immune system leads to production of RF. About 3% of general population is positive for rheumatoid factor and the prevalence increases with increasing age. RF positivity is one of the classification criteria for diagnosis of RA and is positive in about 70% cases of RA. Higher titers (Nx3) are more significant. It has sensitivity (possibility of a positive test in a person having disease) of 80% and specificity (possibility of a negative test in a person without disease) of 95%. Its negative predictive value is 95% whereas positive predictive value is only about 7-10% i.e. 7-10 out of 100 RF positive patients are likely to have RA. RA is a clinical diagnosis and positive predictive value increases to almost 90 in selected cases of recent onset polyarthritis. Quantitative readings must be obtained and levels above 40 IU/ml can be considered as significant. RF positivity indicates poorer prognosis and higher incidence of systemic and extra-articular features. RF should be used only for diagnosis of RA and serial measurements are not indicted for monitoring the disease.

Anti-cyclic Citrullinated Peptide Antibodies (ACPA)

ACPA are antibodies found to be associated with RA. They include various autoantibodies such as antiperinuclear factor, antifilaggrin and antikeratin. They target citrullinated peptides; citrullin being an amino acid formed by de-amination. ACPA are reported to be more specific (90-95%) than RF for diagnosis of RA whereas sensitivity is similar. They are predictive of an erosive disease. These antibodies can become positive 3 to 6 years prior to clinical onset of RA. The test can therefore be used for diagnosis of early RA. RF plus ACPA positivity has specificity of 96% and sensitivity of 48% for diagnosis of

RA. ACPA can also be used to differentiate RA from other rheumatoid factor positive conditions such as hepatitis C associated arthritis, other viral arthritides and fibromyalgia. High titers of these antibodies indicate worse clinical outcome and need for early aggressive management. RF positivity in addition to ACPA positivity, however, does not help in prognostication of RA.

Anti-Streptolysin O (ASO) titer

This test is directed against extra cellular products found in supernatant broth of culture of beta haemolytic streptococci. ASO titer test should be ordered only when diagnosis of acute rheumatic fever (ARF) is suspected (modified Jones criteria). A positive ASO titer indicates nonspecific immune stimulation due to past streptococcal exposure resulting in polyclonal gammopathy. A four-fold rise (320 Todd units in children) is diagnostically significant. These titers start rising about 7 days after infection, peak at 3-5 weeks and gradually return to baseline over next 6-12 months. These titers may rise in infections caused by other streptococci (e.g. sore throat, skin infections, and scarlet fever) and bacteria producing ASO-like products. ASO titers are of no value in nonmigratory arthritis especially in adults. It can be normal in about 20% cases of ARF. The sensitivity can be further improved up to 95% by testing other streptococcal products viz. antiDNase-B and antistreptokinase.

Uric acid

Uric acid is the strongest antioxidant that body produces. Serum uric acid is raised in conditions of fast cell turnover or slowed renal excretion. Most hyperuricaemias are idiopathic or primary. Many drugs such as low dose aspirin, diuretics (except spironolactone), ethambutol and theophyllin cause hyperuricemia. Hyperuricemia is a part of metabolic syndrome along with diabetes mellitus, hypertension, obesity, atherosclerosis and stress. Premenopausal females do not develop gout because estrogens are uricosuric. Uric acid estimations should not be ordered in children and menstruating females unless genetic defect of uric acid metabolism is suspected.

LE cell phenomenon

This is an outdated test and should not be ordered for.

Anti-nuclear antibodies (ANA)

ANA are diverse group of auto antibodies directed against components of cell nuclei and are positive in about 30% cases of RA. ANA-positive RA patients

have more severe disease and poorer prognosis. Other systemic autoimmune diseases such as SLE, Sjogren's syndrome, scleroderma, thyroiditis and chronic active hepatitis also show positive ANA. . About 5% of normal population, especially elderly, have low titer positive ANA. ANA test must be done by immunofluorescence (IF) method and positivity reported in terms of intensity and pattern (speckled, nucleolar, homogenous, etc) of IF. Higher titers (1:100 or more) are more useful for diagnosis. ELISA method is less useful as it gives frequent false positive as well as negative reports. ANA test or autoantibody panels should not be used to screen a patient with arthralgia. As the titers do not correlate with disease activity, repeating the test in a diagnosed case is of no value. A negative IF ANA test excludes diagnosis of an autoimmune disease and further testing such as ANA blot test (for differentiating antibodies) is not warranted.

Anti ds-DNA antibodies

This test is positive in 80-90% patients of SLE but can also be positive in some other inflammatory rheumatologic diseases. The test is more specific than ANA for diagnosis of SLE and correlates with disease activity (more severe disease) as well as renal involvement. It should ideally be done by Farr assay method and expressed as IU/ml. ELISA method can give false positive results.

HLA B27

HLA B27 is a genetic marker normally present in 8-10% of normal population. The diagnosis of ankylosing spondylitis (AS) and other spondyloarthritides needs to be considered in cases of asymmetric large joint arthritis associated with inflammatory back pain. 83-94% of Indian patients of AS are HLA B27 positive. In view of high prevalence in general population, it cannot be a diagnostic test for AS in absence of typical inflammatory back pain. HLA B27 positive patients are more likely to have spinal, ophthalmic and cardiac disease. HLA B27 is an expensive test and must be cardiac used in selected patients with incomplete manifestations of disease. AS affects less than 0.1% population and indiscriminate ordering of this test can be misleading.

Liver function tests

These are often ordered to assess baseline status and monitoring toxicity due to drugs like methotrexate, sulphasalazine and azathioprine. Serum protein estimation indicates appropriate functioning of liver cells; raised SGPT (ALT) and SGOT (AST) indicate hepatocellular injury whereas raised alkaline phosphatase indicates dysfunction of bones or biliary collecting system.

Renal function tests

These are ordered to assess baseline status and monitoring toxicity or dose adjustments of some drugs such as non-steroidal anti-inflammatory drugs. Simple tests such as urine examination, blood urea and serum creatinine can indicate renal involvement at an early stage. Deterioration of renal function may be asymptomatic during initial stages. These tests are useful in detecting renal involvement in various rheumatic diseases such as SLE and vasculitis. They are also useful during follow-up period for suitable modifications in therapeutic regimen.

Synovial fluid examination

Examination of fluid aspirated from a swollen joint is invaluable in the diagnosis of inflammatory, septic and crystal-induced arthritis as well as haemarthrosis. Fluid must be examined immediately after aspiration and cultured for isolation of pathogenic organisms. Synovial biopsy is usually required in cases of monoarthritis. Arthroscopic biopsy has better chances of positive results.

Radiology

X-Rays are necessary for detecting bone erosions, sclerosis, joint space narrowing and other changes for diagnosis of arthritis. There are many other situations where X-Rays of various body parts may be required. Obtaining appropriate views and reading of X-Rays requires adequately trained personnel. Indiscriminate use of X-rays should be avoided as there is a possibility of radiation hazard. Natural background radiation to Indian population is estimated to be 2.299 mSv (millisievert) per year. X-Ray of spine, extremities and chest has radiation exposure of 1.5 mSv, 0.001 mSv and 0.1 mSv respectively. X-Rays should, therefore, be ordered only if required. Pregnant patients must avoid X-Ray and CT examinations.

Musculoskeletal ultrasound and MRI provide invaluable information about synovitis in doubtful cases. MRI of spine should be reserved for those patients in whom surgery is planned. MRI of thigh is useful in cases of polymyositis. Computerised tomography of chest suspected interstial pneumonia, angiography and PET-scan in suspected vasculitis are other investigation required in special circumstances.