

## RHEUMATOLOGY NOTES

### HLA ASSOCIATIONS

The **HLA** system plays a role in antigen presentation and self recognition. HLA A, B and C are all encoded by MHC class I, not class II. Class II MHC molecules encode HLA D, which serve as antigen recognition molecules for T helper cells.

**HLA B8, DR3 and DW3** are associated with autoimmune hepatitis and Sjogren's syndrome.

**HLA-B5, HLA -B51 and HLA-DR5** are associated with Behcet's syndrome.

Decreased **HLA DR2** is associated with narcolepsy,

**HLA DR3** is associated with many autoimmune conditions, autoimmune adrenalitis (Addison's)

Increased **HLA DR4** is associated with rheumatoid arthritis, autoimmune adrenalitis (Addison's)

The most commonly found HLA in coeliac disease (almost 90%) is **HLA DQ2** and **HLA DQ8**.

**HLA B27** is commonly associated with ankylosing spondylitis, reactive & psoriatic arthritis, Reiter's syndrome and Whipple's disease.

### OSTEOMALACIA AND OSTEOPOROSIS

**Osteomalacia** is characterized by a low serum calcium and phosphate with elevated serum alkaline phosphatase. Osteomalacia may be caused by deficiency of vitamin D or phosphate deficiency. Malabsorption syndromes, renal failure and liver disease can result in vitamin D deficiency.

*Looser's zone* are linear areas of low density surrounded by sclerotic borders, which are a feature of osteomalacia.

In adults, treatment is with a daily dose of *calciferol* (20-25 micrograms).

Causes of **osteoporosis** are :

postmenopausal women

Cigarette smoking

eating disorders such as anorexia nervosa or bulimia

hypocalcaemia

heavy alcohol consumption

corticosteroids /Cushing's syndrome

anticonvulsants

**Medications for Osteoporosis:**

Calcium and vitamin D

oestrogen replacement

selective oestrogen receptor modulator (SERM)  
bisphosphonates

The **T score** is usually used to make treatment decisions using standard deviation (SD). The SD measures the difference between the BMD and that of a healthy young adult (the reference value). Every -1 SD ("minus 1 standard deviation") equals a 10 to 12% decrease in bone density. T score results are classified as follows:

A T score between 0 and -1 standard deviation (SD) is considered to be normal.  
A T score between -1 and -2.5 SD is classified as osteopenia (low bone mass).  
A T score of -2.5 SD or less is classified as osteoporosis (very low bone mass).

**Osteopetrosis** is caused by increased bone density due to defective osteoclastic activity.

## **GOUT AND PSEUDOGOUT**

Pseudogout – positively birefringent crystals  
Gout – negatively birefringent crystals

**Pseudogout** causes are:

Haemochromatosis  
wilson's disease  
alkaptonuria (ochronosis)  
hypothyroidism  
hyperparathyroidism  
hypomagnesaemia  
hypophosphataemia

In **gout**, serum uric acid is elevated in 50% of patients, and often not so in an acute flare up. Inflammatory markers are often raised and the patient may be pyrexial in acute gout. Synovial fluid analysis should be undertaken without delay.

**Gout** is associated with :

Hypertriglyceridaemia  
diabetes  
obesity  
Excessive alcohol use  
chronic renal failure  
hypothyroidism  
hyperparathyroidism  
myeloproliferative  
lymphoproliferative disease  
psoriasis

**Drugs reducing uric acid levels in Gout:**

xanthine oxidase inhibitor (allopurinol) or a uricosuric drug (sulfapyrazone)

**Uric acid** results from the breakdown of purines. Purines are found in many foods, for example: Beer and other alcoholic beverages. Anchovies, sardines in oil, fish roes,

herring, Yeast, Organ meat (liver, kidneys, sweetbreads), Legumes (dried beans, peas).

## **RHEUMATOID ARTHRITIS**

**Rheumatoid arthritis** causes subcutaneous nodules over the elbows, swelling of the wrists, ulnar deviation at the metacarpophalangeal joints, Butoinneire's deformity, dinner fork deformity and swelling of the proximal interphalangeal joints.

Periarticular erosions on the X ray are suggestive of **rheumatoid arthritis**.

**Disease Modifying Anti Rheumatic Drugs (DMARDs)** used in Rheumatoid arthritis. D-penicillamine, gold, antimalarials, chloroquine, sulfasalazine, leflunomide, methotrexate. NSAIDs are important in symptom relief, but do not prevent disease progression.

**Anti-TNF drugs** are this group infliximab, etanercept and adalimumab. The criteria for treatment are that the patient has been treated with at least two DMARDs (disease-modifying) drugs but continue to have active rheumatoid arthritis.

**Felty's syndrome** consists of a triad of neutropenia, hypersplenism and rheumatoid arthritis,

The pulmonary complications of **rheumatoid arthritis** are :  
pulmonary fibrosis (interstitial lung disease)  
bronchiolitis obliterans with organizing pneumonia  
bronchiectasis  
interstitial pneumonitis secondary to drugs  
exudative pleural effusions  
Caplan's syndrome (pneumoconiosis, pulmonary nodules)

## **OTHER ARTHRITIS**

**Psoriatic arthritis** presents as several forms:  
symmetrical polyarthritis  
arthritis involving DIP joints  
asymmetrical oligoarthritis  
including dactylitis  
Ankylosing Spondylitis type HLA B27 positive  
sacroilitis  
arthritis mutilans

### **Osteoarthritis**

*Bouchard's nodes* are proximal interphalangeal nodes.  
*Heberden's nodes* are distal interphalangeal nodes.

X ray features of osteoarthritis are:  
joint space narrowing

osteophytes  
subchondral sclerosis  
subchondral cysts

**Juvenile chronic arthritis** is rheumatoid factor negative. Commonest type is Still's disease. Peaks of disease are about 5 years and 15 years of age. A high swinging fever is typical. An erythematous rash can occur, but it is non purpuric. Haematuria is not typical. Certain forms can involve only one or two large joints only. Different classifications are systemic, pauciarticular and polyarticular. Diagnostic criteria include high fever, hepatomegaly, splenomegaly, lymphadenopathy, serositis (pleuritis, pericarditis), leucocytosis. Bone destruction and micrognathia occurs.

**Gonococcal arthritis** classically presents with a hot joint on a background of a migrating polyarthropathy. It affects women more frequently than men (4:1) and its highest incidence is among sexually active adolescent girls. There is also increased risk during menstruation and pregnancy. Two forms of arthritis exist -- one with skin rashes and multiple joint involvement, and a second, less common, form in which disseminated gonococemia leads to infection of a single joint (monoarticular) and joint fluid cultures are positive.

## VASCULITIS

### **Positive ANCA :**

PR3 (Wegener's) and MPO (microscopic polyangitis)

**Wegener's** affects small vessels particularly in the kidneys. Flare ups can vary with season. **Takayasu's** and giant cell arteritis both affect large vessels. **Churg Strauss** patients present with asthma and eosinophilia.

**Polyarteritis nodosa.** PAN causes transmural necrotizing inflammation of small-sized or medium-sized muscular arteries. PAN is a rare condition. Although the causes are unknown in most cases, there is an association with: Hep B virus, Hep C virus, HIV, Cytomegalovirus, Parvovirus B19 and Human T-lymphotrophic virus. Approximately 20% of patients with classic PAN are positive for P-ANCA. Steroids (prednisolone) and immunosuppressive (cyclophosphamide) medications form the backbone of therapy. Plasma exchange is useful as a second-line treatment in PAN refractory to conventional therapy.

The American College of Rheumatology (ACR) has proposed 6 criteria for diagnosis of **Churg Strauss syndrome**. The presence of 4 or more criteria yields a sensitivity of 85% and a specificity of 99.7%.

These criteria are

- (1) asthma (wheezing, expiratory rhonchi)
- (2) eosinophilia of more than 10% in peripheral blood
- (3) paranasal sinusitis
- (4) pulmonary infiltrates (may be transient)

- (5) histological proof of vasculitis with extravascular eosinophils
- (6) mononeuritis multiplex or polyneuropathy

## **TENDON & FASCIA**

*De Quervain's tenosynovitis* is inflammation of the abductor pollicis longus and extensor pollicis brevis. *Finkelstein's test* is positive. This is performed with the thumb flexed across the palm of the hand, asking the patient to move the wrist into flexion and ulnar deviation. This stresses the tendons of abductor pollicis longus and extensor pollicis brevis and reproduces the pain of de Quervain's tenosynovitis.

*Supraspinatous tendonitis*: pain during abduction with limitation of movement is suggestive. Palpation or compression around the greater tubercle of the humerus causes tenderness.

**Eosinophilic fasciitis** is a disorder characterized by peripheral eosinophilia and fasciitis. Swelling and progressive induration of the skin associated with aching of the extremities and occasional morning stiffness develop over a period of weeks. The distribution most often is in the upper extremity, proximal and distal to the elbow, and in the lower extremity, proximal and distal to the knee. Onset may be acute following some sort of strenuous exercise, or it may be subacute. The diagnosis is confirmed by deep biopsy from skin to muscle.

## **DRUGS**

**Methotrexate** may lead to macrocytosis as a result of B12 or folate deficiency. It may also be associated with bone marrow suppression, causing leucopenia or thrombocytopenia. Methotrexate may also cause mouth ulcers, stomatitis, cough and dyspnoea and rarely, a severe pneumonitis.

**Allopurinol** blocks uric acid production and is the drug most often used in long-term treatment for older patients and overproducers of uric acid. Allopurinol is taken orally once a day in doses of 100 mg to 600 mg, depending on the patient's response to treatment. Between 3% to 5% of patients experience leukopenia, thrombocytopenia, diarrhea, headache, and fever.

Hydralazine, procainamide, isoniazid, chlorpromazine, D penicillamine & methyl dopa can result in **drug induced lupus**. Hydroxychloroquine and chloroquine are used to treat SLE.

## **MISCELLANEOUS**

Causes of **sacroilitis**:

ankylosing spondylitis

Crohn's disease

Whipple's disease

ulcerative colitis

septic arthritis

TB

Wegener's granulomatosis

Causes of **mononeuritis multiplex** are:

Rheumatoid arthritis

amyloidosis  
diabetes  
leprosy  
sarcoidosis  
Churg Strauss  
Wegener's granulomatosis  
Polyarteritis nodosa

Causes of **avascular necrosis** of the bone:

SLE  
Nephritis  
vasculitis  
long term steroids  
sickle cell disease

**Causes of Charcot's joints:**

diabetic neuropathy,  
syphilis  
syringomyelia  
leprosy

**Causes of Iritis:**

Behcet's disease  
Reiter's syndrome  
ankylosing spondylitis  
sarcoidosis

**Ankylosing Spondylitis**

The male:female ratio is 5:1 in ankylosing spondylitis. HLA B27 is more prevalent among caucasians. The typical patient is the young male who complains of morning back (spinal involvement) stiffness.

**Antiphospholipid syndrome** (APS) is a disorder characterized by recurrent venous or arterial thrombosis and/or fetal losses associated with typical laboratory abnormalities. It is also known as **Hughes' syndrome**. These include persistently elevated levels of antibodies directed against membrane anionic phospholipids (ie, anticardiolipin [aCL] antibody, antiphosphatidylserine).

Vascular thrombosis - DVT, MI, CVA or miscarriages may occur. Other features are nonthrombotic neurologic symptoms, such as migraine headaches, chorea, seizures, transverse myelitis, Guillain-Barré syndrome, thrombocytopenia or hemolytic anemia, Livedo reticularis, Avascular necrosis of bone and Pulmonary hypertension. Aspirin or warfarin is recommended for patients with thrombotic syndromes.

A positive ANA (speckled pattern), raised CK and positive anti RNP antibody suggests **mixed connective tissue disease**.

**AntiRo antibody** is also associated with *congenital complete heart block*. When congenital complete heart block occurs, SS-A antibodies are almost always present in maternal and fetal serum (maternal anti-Ro(SS-A) antibody crosses the placenta).

**Behcet's syndrome** is classically characterized as a triad of symptoms that include recurring crops of mouth ulcers (called aphthous ulcers), genital ulcers, and uveitis. The ulcers are usually painful. The disease is more frequent and severe in patients from the Eastern Mediterranean and Asia than those of European descent. Eye manifestations may result in blindness. In addition, iritis, retinal vessel occlusions and optic neuritis can be found. *Hypopyon* uveitis (pus in the anterior chamber of the eye), which is considered the hallmark of Behçet's disease, is in fact a rare manifestation. CNS vasculitis involvement may lead to TIA, meningoencephalitis, parkinson's and dementia. Vascular thrombosis occurs in about 10% of patients. The arthritis of Behçet's disease is usually intermittent, self-limited, not deforming and localized to the knees and ankles. A positive *pathergy test* refers to skin injury by needle prick leads to a papule or pustule formation in 48 hours.

**Dermatomyositis:** Causes proximal muscle weakness, dysphagia and raised muscle enzymes. This is associated with *Gottron's papules* and also a heliotrope rash around the eye. The condition is associated with carcinoma of the breast, lung, ovary and bowel. **Dermatomyositis** is most frequent in women, with a male:female ratio of 1:2, and has its peak-incidence in spring and summer. The presence of a rash plus another three or four criterias (proximal and symmetric muscular weakness, elevation of muscular enzymes, inflammatory changes in muscle biopsy or electromyography) confirms the diagnosis.

**Discoid lupus erythematosus:** Lesions are discrete plaques, often erythematous, scaly, with extension into hair follicles. These lesions can occur on the face, scalp, in the pinnae, behind the ears or on the neck. There can also be active indurated erythema and central atrophic scarring.

**Familial Mediterranean fever** is an inherited condition characterized by recurrent episodes of painful inflammation in the abdomen, chest, or joints, fevers and rash. The first episode usually occurs by the age of 20 years, but in some cases, the initial attack occurs much later in life. Familial Mediterranean fever primarily affects populations originating from the Mediterranean region, particularly people of Armenian, Arabic, Turkish, and North African Jewish ancestry. A buildup of amyloid proteins occurs in some cases of familial Mediterranean fever and can lead to renal failure if left untreated. AA amyloidosis commonly involves the kidneys, spleen and GI tract. Colchicine given prophylactically in FMF offers some protection against the development of amyloidosis in most patients.

**Haemochromatosis** is associated with chondrocalcinosis, which commonly affects the 2nd and 3rd metacarpophalangeal joints.

**Hypertrophic osteoarthropathy** (or hypertrophic pulmonary osteoarthropathy when there is mesothelioma or bronchogenic carcinoma associated) is associated with conditions such as liver cirrhosis, ulcerative colitis, whipple's disease and crohn's disease. X rays show periosteal reaction at the ends of the radius and ulnar bones suggestive of periostitis.

**Henoch-Schönlein purpura (HSP)** is a systemic vasculitis mostly seen in children. It is a multisystem disorder involving the skin, joints, gastrointestinal and renal tracts.

Aetiology is unknown, but the syndrome is often preceded by infections such as Group A beta hemolytic streptococcal respiratory tract infection, Campylobacter jejuni, Mycoplasma pneumoniae and viruses such as varicella, hepatitis B, Epstein-Barr virus, and parvovirus B19. Pathology is due to intravascular deposition of IgA immune complexes with activation of complement and leucocyte infiltration. Patients often present with a purpuric rash usually involving the buttocks and lower limbs, arthralgia and joint swelling, severe colicky abdominal pain and tenderness caused by vasculitis-induced thrombosis in the gut.

Renal involvement commonly presents as microscopic haematuria and proteinaemia. The most serious long-term complication from **HSP** is progressive renal failure.

**Limited cutaneous scleroderma** is also known as CREST syndrome (calcinosis, Raynaud's, (o)esophageal dysfunction, sclerodactyly, and telangiectasia. 'Limited' refers to the extent of skin involvement limited to the forearms and face. They generally develop pulmonary hypertension rather than pulmonary fibrosis, leading towards breathlessness. Renal hypertensive crisis is more common in diffuse systemic sclerosis and pulmonary hypertension is more common in limited cutaneous scleroderma

### **Polymyalgia Rheumatica**

A high ESR, shoulder stiffness and pain, age >65, weight loss and depression are features which contribute to diagnostic criteria.

There is NO weakness.

Muscle enzymes and EMG are typically normal

If there is a raised ESR, polymyalgia rheumatica is far more likely than fibromyalgia. 10 mg of prednisolone will suffice for PMR. At the other end of disease spectrum, Giant Cell Arteritis required up to 60 mg of prednisolone to suppress vasculitis

**Reiter's syndrome** is urethritis, conjunctivitis, seronegative arthritis (cannot see, cannot pee, cannot climb a tree). The typical patient is a young man with recent urethritis or dysentery. The seronegative arthritis is usually a mono or oligoarthritis.

Other features are anterior uveitis, keratoderma blenorrhagica (brown abscesses on palms and soles), mouth ulcers, plantar fasciitis and archilles tendinitis (enthesopathy), circinate balanitis (painless rash) and aortic incompetence. The arthritis may relapse or remain chronic. Management is usually with rest and NSAIDs.

**Reflex sympathetic dystrophy** occurs following trauma to an injured part of the body, and can progress to other parts. It is due to autonomic nervous system dysfunction. Symptoms of extreme pain and burning can occur. Analgesics are often unhelpful.

**In Paget's disease**, onset of symptoms is usually insidious, with pain, stiffness, bone deformity, headaches, decreasing auditory acuity, and increasing skull size.

Signs may be bitemporal skull enlargement with frontal "bossing," dilated scalp veins, nerve deafness in one or both ears, angioid streaks in the fundus of the eye, and anterolateral bowing of the thigh or leg with warmth and periosteal tenderness.

Pagetic lesions are metabolically active and highly vascular and may lead to high-output heart failure. Deformities may develop from bowing of the long bones or osteoarthritis of adjacent joints.

Pathologic fractures may be the presenting finding. Characteristic x-ray findings include increased bone density, abnormal architecture, cortical thickening, bowing, and overgrowth.

Biochemistry includes elevated serum *alkaline phosphatase* (or bone-specific alkaline phosphatase) and increased urinary excretion of pyridinoline cross-links. *Serum calcium and phosphorus levels usually are normal*, but serum calcium may increase during bed rest.

**Pott's disease** is tuberculous infection of the spine with associated collapse of the vertebral body. Signs and symptoms include: Localised back pain, Paravertebral swelling, Neurological signs including paraplegia.

Drug treatment (antituberculous drugs) is generally sufficient for Pott's disease, with spinal immobilisation if required. Surgery is required if there is spinal deformity or neurological signs of spinal cord compression.

**Sarcoidosis:** The most common form of joint involvement in sarcoidosis is large joint involvement of lower limb. This is usually a symmetrical oligoarthritis associated with erythema nodosum and bilateral hilar lymphadenopathy.

**Sjogren's syndrome:** history of dry eyes (keratoconjunctivitis sicca) and joint pains with strongly positive RhF. Ro is also known as anti ssA and La is known as anti ssB antibody, both are diagnostic tests for Sjogren's.

**Takayasu's arteritis** is a large vessel vasculitis of unknown origin. The vasculitic process involves structures such as the aorta, great vessels, the sclera and the cardiac conduction tissues. Women are affected more than men, usually in the second and third decades of life. Presentation is often with symptoms such as fever, weight loss, night sweats and arthralgias. Symptoms related to ischaemia may include ischaemic stroke, visual disturbances and claudication.

**X-linked hypophosphataemic Vit D resistant rickets**, serum phosphate is low and urine phosphate is high due to inappropriate renal phosphate wasting. Serum parathyroid levels are usually normal or slightly elevated. Clinically, the most obvious of these aspects is the effect on bone formation and growth that causes very severe rickets, especially in affected males. Treatment is with oral phosphate (difficult to tolerate) and high dose activated Vitamin D.