RHEUMATOLOGY

General Approach to Rheumatic Disease

The rheumatology patient may present with weakness, swelling of joints, stiffness, inability to perform usual activities, or a combination of any of these. It is important to determine time course and distribution – this may be sufficient to arrive at a preliminary diagnosis:

1. **Acute polyarthritis** – note that benign causes predominate
   a. Infective – rubella, mumps, hepatitis
   b. Hypersensitivity – erythema nodosum, serum sickness, Henoch-Schonlein purpura
   c. Onset of chronic inflammatory polyarthritides

2. **Chronic polyarthritis**:
   a. Osteoarthritis
   b. Inflammatory polyarthritis – rheumatoid arthritis and others:
      i. Spondyloarthritis – ankylosing spondylitis, psoriatic and reactive arthritis, IBD
      ii. Post-infective arthritides – rheumatic fever, ‘reactive arthritis’
      iii. Unusual presentation of monoarthritis – infective arthritis, crystal deposition
      iv. Connective tissue – SLE, scleroderma, dermatomyositis, polymyositis, PAN

3. **Acute monoarthritis**:
   a. Trauma
   b. Crystal deposition – monosodium urate (gout), calcium pyrophosphate (pseudogout)
   c. Infective arthritis – staphylococcus, gonococcus, pneumococcus
   d. Others – spondyloarthritis, rheumatoid arthritis, juvenile chronic arthritis

4. **Chronic monoarthritis**:
   a. Osteoarthritis – primary or secondary to trauma/occupation/over-use
   b. Inflammatory monoarthritis – spondyloarthritis, chronic infection (TB)
   c. Regional or widespread pain syndromes – fibromyalgia, PMR, polymyositis

Clinical assessment should include clinical, laboratory, histological and radiological features

1. **History** – race, age, sex, pattern of joint involvement, joint stiffness, injury, infection, associated features in skin/eyes/spine, muscles, bursae, tendons, bowel, urethra
2. **Examination** – nodules, tophi, psoriasis, vasculitis, rash, lymph nodes, eyes, pleura, pericardium, heart, tendon sheaths, bursae, joints
3. **Laboratory investigations**:
   a. Blood tests:
      i. FBC, ESR – anaemia and leucocytosis (inflammation, drugs), leucopaenia (autoimmune, drugs), ESR (increases with age – CRP doesn’t)
      ii. Uric acid – gout, drugs (diuretics, anti-TB, cyclosporin), high protein turnover
      iii. Serology, tissue typing (HLA-B27), serum proteins
         1. Streptococcal antibodies >200 or rising titres of serial sera (>4x)
         2. Antinuclear factor (>1:80) – 99% of SLE, but not specific
         3. Anti-DNA antibodies – raised titre suggestive of SLE
         4. Complement C3/C4 – low levels seen in SLE, rheumatoid arthritis
         5. Rheumatoid factor – 5% normal people, 50-85% of patients with RA
   b. Synovial fluid – cells, differential, glucose, protein, crystals, culture, biopsy
      i. Normal WBC <200 cells/mm³
      ii. OA 200-10,000/mm³, RA 5000-75,000/mm³, septic arthritis >50,000/mm³
   c. Urine – protein, sugar, casts, cells, culture
4. **Radiology** – choice of joints depends whether the X-ray is for diagnosis or assessment

Guidelines:

1. **Screening questions**:
   a. “Do you have any pain or stiffness in your arms?”
   b. “Do you have any problems going up or down steps?”
   c. “Can you dress yourself completely without any difficulty?”
2. **Key points to elicit in a rheumatologic history**:
   a. Time course
   b. Distribution
   c. Extra-articular features
   d. Functional impact
3. **Examination – GALS**
Rheumatology

- Rheumatoid Arthritis

Rheumatoid arthritis is a symmetrical inflammatory arthritis that tends to affect the small joints of the hands and feet, though other joints may also be involved (particularly the cervical spine).

1. Epidemiology:
   a. It affects 1-2% of the population, though severe RA probably only affects 0.2-0.5%
   b. More common in females (4:1) although after the age of 60 incidence is equal
   c. Can occur at any age, with a peak incidence at 30-60 years
   d. Less common and less severe in Maori and Pacific Islanders (different HLA-DR4)
   e. 90% do not have a family history, but having a first degree relative increases risk 4x

2. Extra-articular features are numerous:
   a. Eyes – keratoconjunctivitis sicca, episcleritis, scleritis
   b. Cardiorespiratory – pericarditis, myocarditis, valvulitis, pleuritis, effusions, bronchiolitis, fibrosing alveolitis, anaemia, hypersplenism (Feltty’s syndrome)
   c. Gastrointestinal and renal – blood loss, renal impairment, side-effects of therapy
   d. Neurological - peripheral nerve entrapment, polyneuropathy, spinal cord compression
   e. Bone and soft tissue – vasculitic ulcers, nail fold infarcts, rheumatoid nodules, muscle wasting, tenosynovitis, nodules, rupture, osteoporosis

Aetiology – idiopathic, but that doesn’t stop us discussing a lot of idiotic detail. Ha, ha.

1. Genetic:
   a. Family and twin (30%) concordance studies show a clear polygenic influence
   b. HLA-DR4 is the main known genetic influence, but represents <10% all aetiologies
      i. RA is associated with an epitope at a part which binds to antigenic peptides
      ii. QKRAA/QRRAA (shared epitope) uniquely able to bind certain antigens
      iii. Identity of antigenic peptides unclear – viral, bacterial autoantigens
   c. Maori, Pacific Island, Japanese and Southern Chinese have protective DR4 subtype

2. Environmental – up to 50% of aetiology is related to environmental or random factors
   a. ? impact of climate and urbanisation
   b. Trigger presumed to be a micro-organism (unusual virus?) but as yet unidentified

3. Pathogenesis
   a. Prevailing theory is that RA is an autoimmune disease mediated by T lymphocytes
      i. Autoantibodies have been found, but these may be 2° to the disease
      ii. Many CD4 T lymphocytes accumulate in synovium ?aetiology
      iii. Molecular mimicry is a popular theory (post-infectious self-reactivity)
   b. Cytokines made by fibroblasts and macrophages may also be involved:
      i. IL-1 and TNF – chondrocyte/osteoclast activation, T and B cell activation
      ii. IL-6 – similar to IL-1, also mediates systemic acute phase response
      iii. IL-8 – chemoattractant, neutrophil activation
      iv. GM-CSF – macrophage activation
      v. VEGF – growth of new blood vessels in the synovium
   c. Tissue effects and contributions:
      i. Cells – immune/inflammatory cells, synovial proliferation (pannus)
      ii. Vascular – endothelial damage in small synovial vessels (2° to free radicals?)
      iii. Nervous – unmyelinated C fibres innervating synovium contain neuropeptides including substance P (potent pro-inflammatory, lymphocyte activator)
   d. Other factors involved:
      i. Immune complexes – B cell activation → Rh factor → IgG binding → C3, C4
      ii. Enzymes – phagocytes → damaging enzymes (collagenase, stromelysin)
      iii. Prostaglandins, leukotrienes – macrophage release → inflammation, pain

Clinical assessment:

1. History – typically a woman in her 40s-50s complaining of pain, stiffness and swelling
   a. Which parts of the hands, feet or other joints are affected and in what distribution?
   b. Stiffness as well as pain? Localised or generalised? Extra-articular features?
   c. Diurnal pattern e.g. morning stiffness (opposite with mechanical problems)
   d. Time course – onset, episode, remitting/relapsing, relentlessly progressive?
   e. Aggravating and alleviating factors, response to therapy, functional assessment

2. Examination:
   a. Examine all joints (not just GALS), determine if there is objective arthritis, confirm distribution and look for swelling (soft tissue, fluid, synovium or tendon sheath)
b. Physical examination:
   i. Extra-articular features e.g. pleural effusion, splenomegaly
   ii. Complications of RA or therapy e.g. anaemia, peptic ulceration
   iii. Other inflammatory diseases inflammatory bowel disease, psoriasis
   iv. Other unrelated diseases affects overall morbidity and therapy choice

3. Severity may be determined by the patient subjective, duration of morning stiffness, number of inflamed joints, tenderness of joints, ESR/CRP, extraarticular features, functional limitation

4. Investigations:
   a. Laboratory:
      i. FBC ↑ WBC, ↑ platelets, ± normocytic anaemia
      ii. LFTs low albumin, raised globulins
      iii. ↑ ESR, ↑ CRP, rheumatoid factor (80%), ANA (15%), HLA-DR type not used
      iv. Synovial fluid ↑ neutrophils, culture ± ve, no urate (gout and RA never coexist)
   b. Radiology – soft tissue swelling, effusions, osteopenia (peri-articular generalized), erosions (marginal), decreased joint space, deformity/alignment, 2° OA

5. Differential diagnosis:
   a. SLE
   b. Psoriatic arthritis
   c. Viral infection – rubella, parvovirus, hepatitis B, arbovirus
   d. Lyme disease (not in NZ)
   e. Other inflammatory arthritis or connective tissue diseases

Management:

1. Conservative treatment
   a. Patient education multidisciplinary, written information, arthritis foundation
   b. Rest and exercise rest/splinting reduces synovitis but note the health cost of prolonged bed rest and possibility of contracture (prevented by ROM exercises)
      i. Advise walking 30 minutes 3x a week – no high-impact exercises
      ii. Swimming is a good option, warm pool preferred (efficacy anecdotal)
   c. Diet and alternative therapies tried by 40% of patients
      i. Conventional balanced diet, no harm in reducing perceived triggers
      ii. Some dietary therapies have been formally tested in controlled studies:
         1. Omega-3 fatty acids small benefit if taken in unpleasant quantity
         2. Green-lipped muscle extract no better than placebo
         3. Collagen variable studies, oral tolerance mechanism
         4. Total fasting effective, malnutrition immunodeficiency. Idiotic.
      iii. Alternative therapies generally do no harm (except economical), except:
         1. Chinese herbs may contain corticosteroids, NSAIDs, heavy metals
         2. Herbal teas may contain hepatotoxic alkaloids
         3. Marijuana (for analgesia, muscle spasm) no medical need defence
   d. Other health professionals:
      i. Physiotherapy functional assessment, education, ROM preservation, hydrotherapy, encouragement with exercise/fitness, topical heat and cold
      ii. Occupational therapy ADL assessment and interventions/aids
      iii. Social worker assessment of disease impact, community resources, accommodation, counselling, family therapy

2. Medical treatment:
   a. General principles:
      i. Old pyramid approach start with simple, safe but limited regimens
         1. Trial for several months, try stronger, more toxic drugs if no response
         2. Analgesia DMARDs, SAARDs immunosuppressants others
      ii. New early aggressive approach irreversible joint damage occurs early
         1. However some patients remit spontaneously have mild disease
         2. HLA-DR4 typing and wrist MRI may identify severe disease
   b. Analgesia:
      i. Paracetamol well tolerated, but limited effects
      ii. Opiates avoid if possible, no effective for musculoskeletal or chronic pain
   c. Anti-inflammatories:
      i. NSAIDs marked inter-patient variation in efficacy and side effects
      ii. COX-2 selective NSAIDS not subsidised, may worsen CV outcomes
iii. Corticosteroids – local injections or systemic therapy (resistant disease)

d. Second-line (disease modifying) anti-rheumatic drugs – choice largely determined by
physician preference. Methotrexate is the most effective/tolerated short term; gold
and hydroxychloroquine are weaker than most, and combinations may be used.
   i. Methotrexate (once a week, small dose) – may inhibit neutrophil enzymes;
adverse effects – cytopaenias, nausea (can give folicate), rash, abnormal
   LFTs, liver and pulmonary fibrosis

   ii. Leflunomide (3x 100mg, then 20mg od) – inhibits enzyme (dihydro orate
   reductase) in lymphocyte pyrimidine synthesis; adverse effects – diarrhoea,
rash, cytopaenias (rarely), teratogenic (use cholestyramine to eliminate drug)

   iii. Sulphasalazine – immunomodulator; adverse effects – nausea, rash,
neutropenia, hepatitis

   iv. Gold (IM weekly to monthly) – may interfere with macrophage function;
adverse effects – rash, ulcers, cytopaenias, nephropathy (proteinuria)

   v. Hydroxychloroquine – alters endocytic vesicle pH in antigen-presenting cells
   ↓ production of macrophage cytokines; adverse effects – retinal toxicity

   vi. Cyclosporin – affects T-cells, dendritic cells, macrophages; adverse effects –
   renal toxicity (often combined with methotrexate, interacts with other drugs)

   vii. D-penicillamine – sulfhydryl amino acid group binds various inflammatory
   molecules; adverse effects – nausea, altered taste, cytopaenias, proteinuria

e. Third-line agents and experimental therapies:

   i. Cytotoxics – azathioprine, cyclophosphamide, chlorambucil

   ii. Monoclonal antibodies to TNF, soluble TNF receptors, recombinant IL-1
   receptor antagonist. Evidence suggests TNF blockers → disease modifying

3. Surgical treatment:

   a. Irreversible bone/cartilage damage → joint replacement, arthrodesis, reconstruction

   b. Repair/transfer of ruptured tendons

   c. Synovectomy

4. Complications (may be disease-related or therapy-related)

   a. Osteoporosis – Ca¹², HRT, vitamin D, bisphosphonates

   b. Depression – counselling, antidepressants, pain management

   c. Peptic ulcer – H2 receptor antagonists, proton pump inhibitors, misoprostol

5. Indications for referral:

   a. Uncertainty in diagnosis

   b. Considering second line therapy

   c. Erosions, bone disease, extra-articular features, other severe disease

   d. Complications needing surgery

   e. Specific treatment problems (e.g. comorbidities)

Prognosis:

1. RA is a chronic disease with remissions and relapses (flares)

2. Long-term outcome is difficult to predict, but as a broad generalisation:
   a. 1/3 → complete and permanent remission
   b. 1/3 → long term, grumbling disease, not impacting too much on their life
   c. 1/3 → relentless severe disease, severe disability, require orthopaedic procedures

3. Predictors of poor outcome – female, severe polyarticular onset, still severe after 3/12, high
   ESR, CRP or rheumatoid factor at diagnosis, early bone erosions, HLA-DR shared epitope

• Osteoarthritis

Osteoarthritis is a chrondopathic (rather than synovial inflammatory) form of arthritis resulting from a
‘final common pathway’ involving both degradation and repair, of a number of different insults that
affect the joints. It is characterised by:

1. Focal loss of articular cartilage → hypertrophic reaction in subchondral bone and joint margin
2. Radiologically – joint space narrowing, subchondral sclerosis, cysts, marginal osteophytosis
3. Clinical manifestations may include use-related joint pain, gelling of joints after inactivity and
   loss of range of joint movement
   a. History and examination – age >50, morning stiffness <30 minutes, crepitus, minimal
   inflammation, bony enlargement, Heberden’s (DIP) and Bouchard’s (PIP) nodes
   b. Laboratory – ESR <40mm/hr, Rh F –ve, non-inflammatory synovial fluid
Aetiology and classification:

1. Aetiology – two current paradigms:
   a. Response to joint injury \( \rightarrow \) initiates degeneration/regeneration of all joint tissues
   b. Accumulation of injury with limited repair ability (evolution of joint usage/shape)
   c. Genetic factors – multigenic (e.g. COL2A1 \( \rightarrow \) type II collagen; vitamin D receptor)
      i. 1st degree relatives have a 2-5 fold increased risk
      ii. A recent twin study has estimated the genetic influence to be 50-65%
      iii. Autosomal dominant pattern for 1st osteoarthritis in females

2. Classification:
   a. Classification by joints involved:
      i. Monoarticular, oligoarticular or polyarticular (generalised)
      ii. Chief joint site (index joint site) and localisation within the joint
   b. Classification into primary (idiopathic) and secondary forms:
      i. Metabolic – ochronosis, acromegaly, haemochromatosis, calcium crystals
      ii. Anatomic – SCFE, epiphyseal dysplasia, Perthe’s, DDH, hypermobility
      iii. Traumatic – major, # through joint, osteonecrosis, joint surgery, chronic injury
      iv. Inflammatory – any inflammatory arthropathy, septic arthritis

Management:

1. Conservative management – note psychosocial status, muscle weakness affect pain/disability
   a. Patient contact and education
   b. General exercise and activity; specific physical therapy exercises
   c. Tapes, bandages, walking aids (sticks, canes), shock absorbing footwear

2. Drug therapy – simple analgesia, NSAIDs, local corticosteroids
   a. Optimal pain control depends on defining the source of the pain (local vs general)
   b. There is limited clinical data about superiority of NSAIDs, and recent studies all
      suggest that most patients can be treated with simple analgesics alone
      i. Consider oral NSAIDs only after simple analgesics
      ii. COX2 inhibitors in those with GI side effects (beware ? increased CV risk)
      iii. Old patients are prone to renal and GI side effects
   c. Intraarticular steroid injections are used for anti-inflammatory effect and may relieve
      pain for up to three months (generally less effective than in RA, however)
      i. Elderly patients may experience transient facial flushing
      ii. Diabetics may have upset glycaemic control for a few days
   d. Other agents:
      i. Hyaluronic acid injections (Synvisc, Hylan) – 3-5 weekly injections may give
         pain relief and mobility for 3-9 months; $500 per course and only for the knee
      ii. Glucosamine, chondroitin sulphate – may increase proteoglycans synthesis
      iii. Matrix metalloprotein inhibitors – experimental, inhibit collagenase

Gout and Pseudo-Gout

Gout is an acute arthritis caused by crystallisation within joints of monosodium urate (breakdown
products of DNA) in a hyperuricaemic patient.

1. Epidemiology:
   a. Usually begins between the ages of 40 and 50, affecting more males (3% vs 0.4%)
   b. Very common in Maori and Pacific Island men (10%) – earlier onset severe disease
   c. Chronic tophaeaceous gout in elderly women taking diuretics is not uncommon

2. Aetiology – error of uric acid metabolism
   a. Increased production:
      i. Congenital – increased PRPP (purine) synthetase activity, HPRT deficiency
         (Kelly Seegmiller syndrome partial, Lesch Nyhan syndrome complete),
         glycogen storage diseases, glucose 6 phosphate deficiency
      ii. Acquired – neoplasia (particularly myeloproliferative or lymphoproliferative
         disorders with high turnover), acute EtOH ingestion, high purine diet,
         rhabdomyolysis, exercise, status epilepticus, iatrogenic, idiopathic
   b. Decreased breakdown:
      i. Diabetic ketoacidosis – organic acids compete with urate for tubular secretion
         (similar for starvation, EtOH intoxication, lactic/salicylate acidosis)
      ii. Hyperparathyroidism, hypothyroidism
      iii. Iatrogenic – thiazide diuretics, levodopa

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3. **Pathophysiology**
   a. Uric acid is normally filtered from blood at the glomerulus, almost totally reabsorbed by the proximal tubule then the balance is excreted by tubular secretion.
   b. If serum urate levels are elevated, monosodium urate crystals precipitate into joints.
      i. Acute attacks are triggered by sudden rises or falls in levels.
      ii. Pain due to activation of Hageman factor → bradykinin and leukocyte accumulation
         (leukocytes try to remove crystals → die → release lysosomal enzymes).
   c. If serum urate levels are elevated, monosodium urate crystals precipitate into joints.
      i. Acute attacks are triggered by sudden rises or falls in levels.
      ii. In between attacks formed crystals may partially dissolve and shed.
3. **Disease progression:**
   a. Sustained asymptomatic hyperuricaemia can persist 20-40 years before → gout.
   b. Initial breaks between attacks, then more frequent, longer and more severe episodes.
   c. Tophi evident usually by 10 years after the initial attack → lifelong disease.

**Clinical assessment:**
1. **Clinical features:**
   a. Symptoms – usually single joint (first MTP joint); hot, painful, difficult to move, peak 24-48 hours after first noticed. If chronic, more joints involved. Low-grade fever.
   b. Signs – area intensely inflamed with shiny red or dusky purple skin (may desquamate on resolution), gouty tophi (olecranon bursae, pinnae of ears, hands and feet).
2. **Investigations:**
   a. Clinical picture is usually diagnostic, as is response to NSAIDs.
   b. Joint fluid microscopy is the gold standard, but difficult to perform.
   c. Serum urate > 600 μmol/L (can fall in an acute attack), ↑ ESR, ↑ neutrophils.
   d. Serum urea and creatinine may show renal impairment.

**Management:**
1. **Acute gouty arthritis** – aim is to relieve pain that is usually very severe.
   a. Drugs – NO ROLE for uricosuric drugs or allopurinol
      i. Oral – NSAIDS ± colchicine (if on anticoagulants) ± prednisone.
      ii. Parenteral – NSAID suppositories, corticotrophin gel, intra-articular steroid.
   b. Rest and protection of joint.
2. **Chronic gout** – after acute attack controlled (may need concurrent therapy in first months).
   a. Indications for treatment – serum urate > 0.54 mmol/L; > 1 attack every 3/12 or > 2/52 loss of work; evidence of renal involvement; visible tophi, joint destruction on X-ray.
   c. Uricosuric drugs (increase renal excretion) – probenecid, sulphinpyrazone.
   d. Allopurinol (xanthine oxidase inhibitor) – start slowly, monitor urate/renal function.
      i. Severe tophaceous gout or high levels of urine uric acid.
      ii. Poorly controlled on uricosurics or intolerance.
      iii. Uric acid kidney stones, acute urate nephropathy or advanced renal failure.
3. **Asymptomatic hyperuricaemia** – correct the cause. Note that drugs not indicated except:
   a. Hyperuricaemia primary, persistent and prolonged.
   b. Complications are likely (serum urate > 0.78 mmol/L).
   c. Patient understands implications and is well motivated.

**Calcium pyrophosphate arthropathy** is an arthropathy associated with deposition of calcium pyrophosphate dihydrate in knees, wrists, shoulders, and hips. It is a disease of the elderly, often associated with osteoarthritis and metabolic diseases (haemochromatosis, hyperparathyroidism).

1. **Clinical presentation:**
   a. Pseudogout – monoarthritis, may be triggered by minor trauma.
   b. Associated with OA – progressive degenerative joint changes without acute episodes.
   c. Subacute arthritis mimicking rheumatoid arthritis – inflammatory component.
   d. Clinically silent – e.g. incidental finding of chondrocalcinosis on X-ray.
2. **Diagnosis:**
   a. Joint aspiration → rhomboid shaped, positive birefringence crystals on phase contrast.
   b. Radiology → chondrocalcinosis in menisci or hyaline cartilage, deposits at triangular fibrocartilage of the wrist.
3. **Treatment:**
   a. Intra-articular steroid injection very useful.
   b. Occasionally colchicine of benefit.
Seronegative Spondarthritides

Ankylosing spondylitis is a chronic progressive arthritis distinguished by its involvement of the sacroiliac and spinal paeophyseal joints, in addition to inflammation of the peripheral joints and tendon attachments (enthesitis).

1. Epidemiology – racial variation, M>F (3:1), early onset 20-40 years
2. Clinical features:
   a. History – nocturnal back pain with morning stiffness, relieved by exercise, sacroiliac joints always involved but may have peripheral arthritis (particularly hips and knees)
   b. Examination – pain on sacroiliac compression, chest expansion <3cm, finger-to-floor (unable), Schober’s test (spinal flexion) <5cm (normal 10cm), occiput to wall (unable)
   c. Complications – iritis (25%), heart block (10%), amyloidosis (6%), aortitis (4%)
3. Investigations:
   a. X-rays – sacroiliac joint irregularity → fusion (may be seen in other spondarthritides)
   b. ↑ESR (80%), HLA-B27 present (96% but also other spondarthritides)
4. Treatment:
   a. Anti-inflammatory medication
   b. Spinal, posture and breathing exercises

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<thead>
<tr>
<th>Rheumatoid Arthritis</th>
<th>Ankylosing Spondylitis</th>
</tr>
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<tbody>
<tr>
<td>Ratio M:F</td>
<td>1:4</td>
</tr>
<tr>
<td>Sacroiliac joints</td>
<td>Rare</td>
</tr>
<tr>
<td>Spinal (axial) joints</td>
<td>Cervical spine often</td>
</tr>
<tr>
<td>Costovertebral joints</td>
<td>Not involved</td>
</tr>
<tr>
<td>Peripheral joints</td>
<td>Invariable – bilateral, symmetrical</td>
</tr>
<tr>
<td>Recurrent iridocyclitis</td>
<td>Not increased</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>Up to 20%</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>Up to 85% adults, 10-20% JCA</td>
</tr>
<tr>
<td>HLA-B27</td>
<td>Same frequency as normal controls</td>
</tr>
</tbody>
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Reactive arthritis (Reiter’s disease) is a post-infectious syndrome after venereal or enteric infection with a range of organisms (Salmonella, Shigella, Campylobacter, Borrelia, Yersinia, Chlamydia):
1. Young men with arthritis (asymmetrical, large joints) and urethritis ± conjunctivitis
2. May also have mucocutaneous lesions (buccal mucosal ulcers, circinate balanitis, keratoderma blennorrhagica), systemic upset (fever, weight loss) mimicking septic arthritis
3. Urethritis and arthritis is enough for diagnosis if gonococcus is excluded

Psoriatic arthritis is an arthritis occurring in seronegative nodule-free patients with psoriasis (up to 7%), presenting with skin lesions (nail pitting, onycholysis), dactylitis and enthesitis
1. Clinical syndromes:
   a. Arthritis indistinguishable from RA (though more DIP involvement)
   b. Asymmetrical peripheral polyarthritis often with predominance of DIP joints
   c. Spondylitis
2. Treatment:
   a. As per RA
   b. Salazopyrin, methotrexate or slow-acting antirheumatic drugs preferred as 2nd line

Enteropathic arthritis is associated with inflammatory bowel disease (ulcerative colitis, Crohn’s):
1. Acute migratory polyarthritis, large joints, parallels activity of bowel disease (14%)
2. AND/OR Non-HLA-B27 sacroiliitis, parallels bowel disease activity (9%)
3. AND/OR HLA-B27 spondylitis, indistinguishable from ankylosing spondylitis (4%)

Arthritis in the Elderly – Polymyalgia Rheumatica and Giant Cell Arteritis

Polymyalgia rheumatica and giant cell arteritis are thought to fall along a continuum, with PMR representing a mild form and GCA a severe form of the disease. While there are clear pathological features in GCA, none have been described in PMR (note 15% have positive temporal artery biopsy).
1. Pathogenesis:
Rheumatology

a. Environmental trigger (?viral) – many have a history of preceding illness
b. Vasculitis in GCA is immunological – CD4 T lymphocytes are implicated
c. Associated with HLA-DRB*04 (all subtypes)

2. Differential diagnosis:
   a. Late-onset RA (note that older patients may have false-positive rheumatoid factor)
   b. Polymyositis – clinical muscle weakness
   c. Prodrome for viral infections
   d. Other systemic illness – neoplasia, metabolic disorders, psychiatric (depression)

Clinical features (italics specific to GCA)
1. History – patient >60yrs, shoulder ± pelvic girdle pain, morning stiffness, systemic features (malaise, weight loss, fatigue), jaw claudication or scalp tenderness, visual loss/diplopia
2. Examination – pain on shoulder abduction, no true weakness/wasting or evidence of inflammatory arthritis, thick/tender temporal artery, arterial bruits, scalp tenderness
3. Investigations:
   a. ESR >40mm/hr, CRP elevated – rapid response to modest doses of steroids
   b. Temporal artery biopsy (low sensitivity due to skip lesions, wrong side biopsied etc.)

Management:
1. Steroids – 10-15mg/day for PMR, 40mg/day for GCA; most for >2yrs (relapse on withdrawal)
2. Steroid-sparing agents (only modest effects) – azathioprine, methotrexate
3. Bone protection – bisphosphonates, Ca+, HRT, adequate vitamin D

Connective Tissue Diseases

Connective tissue diseases are characterised by inflammation, autoimmune pathology (frequently ANA positive, RF positive), multisystem/multiorgan involvement. Note that many have organelle-specific autoantibodies, and assessment/management basically needs early specialist referral.

1. Epidemiology:
   a. Rheumatoid arthritis – 3F:1M; prevalence 1000-3000/100,000
   b. SLE – 9F:1M; Polynesians 51/100,000, Europeans 15/100,000
   c. PSS – 3F:1M; annual incidence 0.4/100,000
   d. PM/DM – 2F:1M; annual incidence 0.4/100,000
   e. PMR – F>M; prevalence 400/100,000 (800/100,000 in >80 age group)

2. Pathogenesis:
   a. Autoimmunity is the main theory, mainly from animal models but also other evidence:
      i. Transplacental transfer – neonatal SLE, heart block (anti-Ro/La)
      ii. Passive serum transfer – thyrotoxicosis in silly researchers, neonatal thyrotoxicosis or myasthenia gravis (maternal anti-TSH or anti-AChR)
   b. Genetic predisposition:
      i. Immunoglobulin genes – autoantibody genes activated by somatic mutations
      ii. T-cell receptor – TCR-Vβ genes used by autoreactive T-cells (? therapy)
      iii. Complement – impaired clearance of immune complexes in SLE
      iv. MHC – many have HLA-B8, -DR3 haplotype, HLA-DR4 in RA, HLA-DQ in DM
      v. Antigen presentation – specialised proteins on the surface of dendritic cells

3. Differential diagnosis:
   a. Infection – SBE, pyogenic infection (immunosuppression may kill these patients)
   b. Granulomatous disease – sarcoidosis, tuberculosis
   c. Malignancy – metastatic, myxoma, leukaemia, myeloma, lymphoma
   d. Metabolic – porphyria, amyloidosis, pulmonary embolus
   e. Drug reaction

Assessment and management:
1. Diagnosis – clues to connective tissue disease:
   a. Musculoskeletal pain
   b. Systemic symptoms – malaise, fatigue, anergia, anorexia, weight loss, fever, ↓mood
   c. Multisystem disease – multiple organs, chronic/episodic illness, specific features
   d. Laboratory abnormalities – ESR, anaemia, ↓PLT, ↓neutrophils, prolonged APTT, ↑CK

2. History:
   a. General – fever of unknown origin, lymphadenopathy, splenomegaly, Raynaud’s
Rheumatology

b. Skin – erythema, nodules, urticaria, purpura, alopecia, sclerodactyly, telangiectasia

c. Eyes – keratitis, uveitis, scleritis, sudden blindness, diplopia

d. Cardiopulmonary – pleuritis, pericarditis, valvulitis, myocarditis

e. Abdominal – peritonitis, nephritis, renal failure

f. Musculoskeletal – arthritis, arthralgia, myositis

g. CNS – amaurosis fugax, headaches, epilepsy, strokes, encephalopathy

3. Investigations:

a. Screening tests – FBC, ER, LFT, U&Es, urinalysis, X-ray, blood culture, RF, ANA

b. Further tests as indicated:
   i. Vasculitis – biopsy (skin, muscle, renal, nerve, temporal artery), angiography
   ii. Others – Hb, Ag, ANA, anti-dsDNA, complement, RF, cryoglobulins, EMG, muscle biopsy, muscle enzymes, creatine clearance, 24hr urine protein, ECG/echocardiogram, ANCA, muscle MRI, pulmonary function, brain MRI

4. Management – bottom line is these are too fucking rare for anyone but a specialist to handle

a. General points:
   i. Accurate diagnosis – extensive investigation, note immediate threats
   ii. Long-term monitoring and collaboration between patients and doctors
   iii. Supportive therapy – anti-depressants, anti-hypertensives, counselling, social services, patient support groups, patient and family education

b. Drug therapy – no specific curative therapy, tailor to the disease/individual:
   i. Analgesia
   ii. NSAIDS – may need gastric protection
   iii. Steroids – need bone protection
   iv. Immunosuppressives – azathioprine, cyclophosphamide (high risk of long-term bladder carcinoma), methotrexate, hydroxychloroquine (reduces lupus rash)
   v. New agents – monoclonal antibodies, soluble receptors, receptor antagonists
      1. Soluble TNF-α receptors bind TNF-α, prevent macrophage activation
      2. TNF-α antibodies neutralise TNF-α

Examples (the bit about not needing to know this is utter bullshit. Last year’s class got screwed):

1. Systemic lupus erythematosus
   a. Epidemiology – females aged 15-40, particularly Polynesians and SE Asians; 85% risk with monozygotic twins, 3% with first degree relative
   b. Pathology – auto-antibodies, phagocytosis by monocytes and macrophages, immune complex deposition, release of inflammatory mediators, vasculitis
   c. Diagnostic criteria:
      i. Clinical – malar/discoid rash, photosensitivity, oral ulcers, arthritis, serositis
      ii. Renal disorder (poor prognosis), neurologic disorder (also poor prognosis), haematologic disorder, immunologic disorder, antinuclear antibodies
      iii. Associated with deposition of Ig and complement at dermo-epidermal junction, Jaccoud’s arthropathy and neuropsychiatric lupus (2° infarction)
   d. Investigations:
      i. Antinuclear antibodies – 100% sensitive for SLE, not completely specific
      ii. Double-stranded DNA antibodies – specific for SLE, may → renal disease
      iii. Drug induced SLE – procainamide, hydralazine (histones targeted by ANA)

2. Systemic sclerosis (scleroderma)
   a. Epidemiology – most common age of onset 20-50 yrs
   b. Pathogenesis unclear – excessive fibroblast collagen → endothelial injury/activation?
   c. Clinical features:
      i. Raynaud’s phenomenon – arteriolar vasospasm (white → blue → red)
      ii. Scleroderma – tightening and thickening of skin
      iii. Musculoskeletal – inflammation (↑CK), arthralgia, erosive arthritis
      iv. Others – dysphagia, reflux, malabsorption, dysmotility, pulmonary fibrosis, pulmonary hypertension, renal failure, acute renal crisis
   d. Disease patterns:
      i. Limited (CREST) – calcinosis, Raynaud’s (many years), oesophageal dysfunction, sclerodactyly, telangiectasia → late pulmonary hypertension
      ii. Diffuse – skin thickening progresses proximally, lung/renal/GI disease

3. Polymyositis/dermatomyositis:
   a. Epidemiology – most common age of onset 20-50 years
b. Clinical features:
   i. Muscles – inflamed, proximal weakness/tenderness
   ii. Skin – rash (photosensitive areas), telangiectasia, Gottron papules on fingers
   iii. Associated with malignancy (paraneoplastic manifestation) in those <50yrs

c. Investigations:
   i. Muscle biopsy – histiocytes, lymphocytes → degeneration, necrosis
   ii. EMG, CXR, high-res CT, muscle enzymes, autoantibodies (Jo-1, PM-Scl)

4. Mixed connective tissue disease – SLE + scleroderma + polymyositis
   a. Investigations – Anti-RNP antibody
   b. Most evolve into full-blown scleroderma/SLE but less likely to develop renal failure

5. Sjogren’s syndrome
   a. Pathology – autoimmune (T-cell mediated ANA) destruction of exocrine glands
   b. Clinical features:
      i. Keratoconjunctivitis sicca – inadequate lacrimal/salivary gland function
      ii. Parotid gland enlargement may → lymphoma
      iii. Others – purpura, renal tubular acidosis, trigeminal neuralgia, lung disease
   c. Disease patterns:
      i. Primary – sicca syndrome
      ii. Secondary – sicca syndrome plus connective tissue disease

6. Anti-phospholipid syndrome – part of the differential for abnormal thrombosis
   a. May occur in SLE or as an isolated syndrome – this is the basis for cross-reactivity of anti-DNA with cardiolipin and false-positive syphilis test (VDRL) in SLE patients
   b. Interfere with coagulation assays and are often detected as prolonged APTT
   c. Present with venous/arterial thrombosis (AP Ab target anticoagulant annexin V → accelerate plasma coagulation), recurrent miscarriages and thrombocytopenia
   d. Treatment – mild-anti-platelet agents → anticoagulation → immunosuppression

Note: rheumatoid factor is best used for the differential diagnosis of inflammatory polyarthritis – it is nowhere near 100% sensitive or specific for rheumatoid arthritis (80% sensitive) and is present following infection and other autoimmune diseases. However, it does correlate with more severe RA.