Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a common chronic inflammatory autoimmune disease characterised by an inflammation of the synovial joints leading to joint and periarticular tissue destruction, as well as a wide variety of extra-articular features (see also the separate Rheumatoid Arthritis and the Lung article).

RA is associated with significant morbidity, including pain and disability. Suppression of inflammation in the early stages of the disease can result in substantial improvements in long-term outcomes. Improvements in the use of existing disease-modifying drugs, the development of new drugs and the better application of a range of therapeutic options including non-pharmacological treatments are important in reducing morbidity and mortality from RA.

About one third of people with RA remain seronegative[1]. Despite awareness of the role of circulating autoantibodies in the development of 'seropositive' RA, the pathogenesis of seronegative RA is poorly understood. Evidence suggests that RA 'serotypes' reflect distinct disease entities that diverge with respect to genetic architecture, cellular pathology and even therapeutic responsiveness[2].

Epidemiology[3]

- One study in the UK found the population minimum prevalence of RA to be 1.16% in women and 0.44% in men[4].
- The incidence of the condition is low, with around 1.5 men and 3.6 women developing RA per 10,000 people per year.
- The overall occurrence of RA is two to four times greater in women than in men.
- The peak age of incidence in the UK for both genders is the 40s, but people of all ages can develop the disease.

Risk factors
RA results from an interaction between genetic susceptibility and environmental factors, including high birth weight, smoking, silica exposure, alcohol abstention, obesity, diabetes mellitus, rheumatoid factor, and anti-citrullinated protein antibody[5, 6].

- Smoking is an important risk factor[7].
- HLA DR4 and DR1 are associated, especially in severe disease.
- There is possible infective aetiology, although no organism has been demonstrated.
- Onset is more common in winter.

Presentation[8]

See also the separate Rheumatological History, Examination and Investigations and Aching Joints - Assessment, Investigations and Management in Primary Care articles.

National Institute for Health and Care Excellence (NICE) guidance emphasises the importance of early diagnosis and treatment[3]. There is evidence that the first 12-week period of the disease is immunologically distinct and represents a unique opportunity to influence the progress of the disease. The challenge for GPs is to recognise early symptoms and refer early. The presentation can be very variable. Constitutional symptoms (eg, profound fatigue, influenza-like symptoms, fever, sweats and weight loss) are common.

- Arthritis:
  - Usually starts as an insidious symmetrical polyarthritis, often with nonspecific systemic symptoms. RA can affect any synovial joint but typically affects the small joints of the hands and the feet. It is usually bilateral and symmetrical in distribution. More joints are affected with progression of the disease.
  - Joint inflammation produces characteristic changes: heat and sometimes redness, swelling, pain, stiffness (especially in the early morning or after inactivity), progressive joint destruction and loss of joint function. Pain, swelling, muscle wasting and damage to joints result in progressive deformity, disability and handicap.
  - Tendon sheaths have synovial linings and inflammation of these can result in tendon rupture.

- Signs of arthritis include:
  - Symmetrical, distal, small joint arthritis involving the proximal interphalangeal, metacarpophalangeal, wrist, metatarsophalangeal, ankle, knee and cervical spine joints.
  - Shoulders, elbows and hips are less commonly affected.
  - Hand deformities, including ulnar deviation, swan neck and Boutonnière's deformity of the fingers, Z deformities of thumbs and piano key deformity of the wrist.
  - Muscle wasting and tendon rupture.
  - Cervical complications (instability of the cervical spine).
  - Occasionally, may present atypically as a monoarthritis, sudden-onset or systemic illness with minimal joint problems at first (especially in men). This is known as 'palindromic RA'.
RA is a systemic disease and there are other manifestations of the disease:
- Eyes: secondary Sjögren’s syndrome, scleritis and episcleritis.
- Skin: leg ulcers especially in Felty’s syndrome (association of rheumatoid factor positive rheumatoid arthritis, neutropenia and splenomegaly). Rashes, nail fold infarcts.
- Rheumatoid nodules: these are common, and may occur in the eyes, may be subcutaneous, and may be in the lung, heart and occasionally the vocal cords.
- Neurological: peripheral nerve entrapment, Atlanto-axial subluxation, polyneuropathy, mononeuritis multiplex.
- Cardiovascular system: pericardial involvement, valvulitis and myocardial fibrosis, immune complex vasculitis. A recent study concluded that there was an excess risk of fatal myocardial infarction compared to the general population [9]. Some RA treatments (eg, methotrexate) have been found to have a protective effect against cardiovascular disease.
- Kidneys: rare, including analgesic nephropathy, amyloidosis.
- Liver: mild hepatomegaly and abnormal transaminases are common.
- Other: thyroid disorders, osteoporosis, depression, splenomegaly.
- Significant associated diseases and susceptibilities can further increase morbidity and mortality - eg, ischaemic heart disease and atherosclerosis, osteoporosis and susceptibility to infections.

Differential diagnosis
See also the separate Acute Monoarthritis and Acute Polyarthritis articles.

- Viral arthritis (eg, parvovirus, rubella, hepatitis B).
- Reactive arthritis (eg, postinfective: throat, gut, sexually acquired).
- Seronegative spondyloarthropathy (eg, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease).
- Connective-tissue disease (eg, systemic lupus erythematosus (SLE), scleroderma).
- Polymyalgia rheumatica.
- Polyarticular gout.
- Osteoarthritis (eg, involvement of the proximal and distal interphalangeal joints, Heberden's or Bouchard's nodes).
- Septic arthritis (particularly if monoarthritis).
- Lyme disease.
- Medical conditions presenting with arthropathy - eg, sarcoidosis, thyroid disease, infective endocarditis, haemochromatosis, diabetic cheiro-arthropathy, paraneoplastic syndromes, multiple myeloma.

Investigations

**Editor’s Note**
July 2018 - Dr Hayley Willacy recommends the recently released NICE guidelines dealing with RA mangement in adults [10]. They suggest that clinicians should refer for specialist opinion any adult with suspected persistent synovitis of undetermined cause. Refer urgently if any of the following apply:
- The small joints of the hands or feet are affected.
- More than one joint is affected.
- There has been a delay of three months or longer between onset of symptoms and seeking medical advice.
Offer to carry out a blood test for rheumatoid factor in adults with suspected RA who are found to have synovitis on clinical examination. Consider measuring anti-CCP antibodies in adults with suspected RA if they are negative for rheumatoid factor. X-ray the hands and feet in adults with suspected RA and persistent synovitis.

Diagnosis is essentially clinical; investigations are important in assessment and exclusion of other possible diagnoses.

**Nonspecific investigations**
- ESR, CRP and plasma viscosity: usually raised but may be normal.
- FBC: normochromic, normocytic anaemia and reactive thrombocytosis are common in active disease. Raised ferritin but low serum iron concentration and total iron binding capacity.
- LFTs: mild elevation of alkaline phosphatase and gamma GT.
- Antinuclear antibody: positive in SLE and related conditions; also in up to 30% of RA patients and weakly positive in up to 10% of the normal population.
- Uric acid/synovial fluid analysis: excludes polyarticular gout.
- Urinalysis: microscopic haematuria/proteinuria may suggest connective tissue disease.

**Specific investigations**
NICE recommends [9]:
- Rheumatoid factor in people with suspected RA who are found to have synovitis on clinical examination. Rheumatoid factor: positive in 60-70% of patients (and 5% of the normal population).
- Anti-cyclic citrullinated peptide (anti-CCP) antibodies in an individual with suspected RA, if the patient is negative for rheumatoid factor, and there is a need to decide about starting combination therapy. Anti-CCP has been found to be more specific than rheumatoid factor in RA and may be more sensitive in erosive disease [11].
• X-ray the hands and feet early in the course of the disease in people with persistent synovitis in these joints. X-rays may show soft tissue swelling, periarticular osteopenia, loss of joint space, erosions and deformity.

Management

See the separate articles on Management of Rheumatoid Arthritis and Disease-modifying Anti-rheumatic Drugs (DMARDs).

NICE has published guidance on the standards of care for people with RA[3]. Early involvement of secondary care is very important for establishing the diagnosis, early use of DMARDs and ensuring full access to all available resources.

Complications

• Adverse effects on work and social life are common[12]. Many people with RA have restricted mobility and difficulties with activities of daily living. Inability to work may occur early in the course of the disease, especially in someone with a manual occupation. Approximately one third of people stop work because of the disease, within two years of onset, and the proportion of people who have stopped work increases with time[3].
• Depression is common.
• Inflammatory conditions other than those involving joint and tendon.
• Vasculitis, vasculitic ulcers.
• Pleurisy, pleural effusions, pulmonary fibrosis.
• Pericarditis, pericardial effusions, myocardial infarction, myocardial dysfunction, myocarditis.
• Lymphadenopathy.
• Dry eye syndrome (keratoconjunctivitis sicca).
• Neuropathy.
• Felty’s syndrome (enlarged spleen and low white cell count); can present with an infection or leg ulcer.
• Amyloidosis (rare).
• Anaemia.
• Orthopaedic complications: carpal tunnel syndrome, tendon rupture (particularly extendors of fingers or thumb), cervical myelopathy (usually after severe and long-standing RA), osteoporosis, articular deformities and functional impairment.
• Infectious complications: increased risk of infections. Pulmonary infection and generalised sepsis are particular risks. Septic arthritis is a rare but serious complication.

Prognosis

• The prognosis is variable. The clinical course is typically periods of exacerbations and remissions but may be mild self-limited disease or a chronic progressive illness. Approximately 40% of patients become disabled after ten years. The prognosis is worse when diagnosis and treatment are delayed.
• A worse prognosis for joint damage and disability is associated with:
  • Age younger than 30 years, male.
  • Insidious onset.
  • Extra-articular manifestations, a large number of involved joints, systemic symptoms, persistent anaemia of chronic disease.
  • HLA-DRB1*04/04 genotype, a high serum titre of autoantibodies (eg, rheumatoid factor, anti-CCP), raised levels of complement C1q.
  • Early X-ray evidence of bone erosions.
  • RA that remains persistently active for longer than one year.
• There is increased mortality, particularly due to cardiovascular disease, infection, vasculitis, and poor nutrition.

Further reading & references

• Guideline for disease-modifying anti-rheumatic drug (DMARD) therapy; British Society for Rheumatology and British Health Professionals in Rheumatology (2008)
• BSR and BHPR guideline for the management of rheumatoid arthritis (after the first 2 years); British Society for Rheumatology and British Health Professionals in Rheumatology (January 2009)
• Rheumatoid arthritis; NICE CKS, August 2013 (UK access only)

3. Rheumatoid arthritis in adults: management; NICE Clinical Guideline (February 2009)
10. Rheumatoid arthritis in adults: management; NICE Guideline (July 2018)

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