RHEUMATOID ARTHRITIS

Definition
- Chronic multisystem disease of unknown cause
- Persistent inflammatory arthritis
- Peripheral joints, symmetric
- Cartilage destruction, bone erosions

Prevalence
- 0.8% (0.3-2.1%)
- M/F = 1/3
- Incidence and severity vary with geographical latitude
- 80% starts between age of 35-50
- >6 times frequent in 60-64 than in 18-29 years of age

Etiology
- Host genetic factors
- Immunoregulatory abnormalities and autoimmunity - Autoinflammation
- Triggering or persisting microbial infection

Genetics
- 4 times more common in 1st degree relatives
- 10% of RA patients will have affected 1st degree relatives
- Monozygotic twins are >4 times concordant than dizygotic

The hypervariable region of the MHC II molecule

HLA alleles associated with RA
- Hypervariable region amino acid sequence: QKRAA

Immunoregulatory abnormalities and autoimmunity
- Immune response to components of joints and revealing antigenic peptides (type II collagen, hsp)
- Rheumatoid factor (RF): immunoglobulin directed against self immunoglobulins

Triggering or persisting microbial infection
- Response to an infectious agent in genetically susceptible host
- Parvovirus B19, M. tbc, rubella, mycoplasma
- „Molecular mimici”:
- EBV QKRAA
- E. coli hsp
- Superantigens of microorganisms (Sta., Stre., M. arthritidis) bind to HLA-DR or Vβ segments of TCR → stimulation of specific Tc-s

Pathology and pathogenesis

Earliest findings
- Microvascular injury, synovial lining hyperplasia, increased number of blood vessels
- Perivascular infiltration by mononuclear cells:
- T cells: CD4+, γδTCR+, CD4+ memory cells, rarely CD8+
• Rarely B cells and plasma cells: RF production, formation of germinal centers

**Further findings**

Further hyperplasia of lining cells, synovial oedema, protrusion into joint cavity, proliferating synovium becomes villous and vascularized → **PANNUS**. The pannus consists of: proliferating fibroblasts, small blood vessels, mononuclear cells.

Synoviocytes invade bone at synovium-bone interface, producing TNF-α and IL-1. These cytokines result in production of metallo-proteinases (collagenase, stromelysin) and PGE2 by synoviocytes → self-destruction of chondrocytes, promote degradation, inhibition of proteoglycan synthesis by chondrocytes, enhancement of Ca resorption from bone.

**Cytokines in rheumatoid inflammation**

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Cytokine involved</th>
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<tbody>
<tr>
<td>Synovial tissue inflammation</td>
<td>IL-1, TNF-α, IFN-γ, IL-6, IL-2, GM-CSF, M-CSF</td>
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<tr>
<td>Synovial fluid inflammation</td>
<td>IL-1, TNF-α, IFN-γ</td>
</tr>
<tr>
<td>Synovial proliferation</td>
<td>PDGF, IL-1, IGF, FGF, TGF-β, EGF</td>
</tr>
<tr>
<td>Cartilage and bone damage</td>
<td>IL-1, TNF-α</td>
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<tr>
<td>Systemic manifestations</td>
<td>IL-1, TNF-α, IL-6</td>
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</table>

**The onset of RA**

- 2/3 of patients: Insidious – fatigue, anorexia, generalized weakness, vague musculoskeletal symptoms
- 10-20% of patients: Acute – rapid development of polyarthritis, often with fever, lymphadenomegaly, splenomegaly
- Rarely: Recurrent (palindromic) acute monarthritis

**Signs and symptoms of RA**

- Initially: pain, swelling, tenderness
- Affected joints: PIP, MCP, wrist, elbow, shoulder, knee, ankle, MTP, atlanto-axial
- Joint involvement: polyarticular and symmetric
- Limitation of motion: pain - aggravated by movement, stiffness - aggravated by inactivity
- Morning stiffness > 1 h duration
- DIP: rarely, lumbar spine: almost never
- Constitutional symptoms: malaise, weakness, easy fatigability, anorexia, weight loss, low grade fever (< 38 °C)

**Late changes of the hands in RA**

- Radial deviation of the wrist and ulnar deviation of the digits, often with palmar subluxation of the proximal phalanges – „Z“ deformity
- Atrophy of interosseal muscles
- Hyperextension of the first IP and flexion of the MCP loss of thumb motility and pinch
- Tenosynovitis of the dorsal wrist: swelling of the metacarpals, extensor tendon erosion and rupture
- Boutonnière (buttonhole) and swan-neck deformities

Knee involvement, Baker’s popliteal cyst
The feet and ankles in RA: plantar subluxation of MTP heads, cock-up deformities of the toes, bursal swelling, hallux valgus

Other joints involved in RA

- Elbows – early flexion contractures
- Shoulders – large synovial cysts, subluxation of the humerus (rare)
- Hips – large effusions, severe pain
- Cricoarythenoid joints – dysphagia, hoarseness
- Olecranon bursitis and rheumatoid nodules

Rheumatoid vasculitis: limited form: leukocytoclastic vasculitis or mild venulitis, aggressive, widespread form: Severe necrotizing vasculitis, digital infarcts, mononeuritis multiplex

Cardiac manifestations: myoepicarditis, inflammatory cellular and rheumatoid nodular infiltrate of the epicardium and myocardium, rheumatoid nodules in the aortic valve cusp, exudative pericarditis

Pulmonary manifestations: pleural effusion (low glucose and complement level), pulmonary nodules, Caplan’s syndrome – diffuse nodular fibrosis

Ophthalmologic manifestations: episcleritis (red eye, mild pain), scleritis, scleromalacia, keratoconjunctivitis sicca (due to Sjögren’s syndrome)

Cervical instability: protrusion of the odontoid process into the foramen magnum, atlanto-axial subluxation

The carpal tunnel syndrome

Laboratory findings in RA

- Elevated ESR and CRP
- Normochromic, normocytic anemia
- Thrombocytosis
- Decreased serum iron and TIBG
- ANA (in 30-40%)
- Specific: Anti-cyclic citrullinated peptide antibodies (anti-CCP) or anti-citrullinated protein antibodies (ACPA)
- RF (in >2/3 of patients)
- Synovial fluid: turbid, reduced viscosity, protein content > 3.0 g/l, slightly decreased glucose concentration, WBC: 5,000 - 20,000/μl, > 75% PMN, decreased CH50, C3, and C4.

RF positivity in diseases other than RA
Autoimmune diseases: SLE, Sjögren’s syndrome, PSS, chronic liver diseases, cirrhosis, cryoglobulinemia, sarcoidosis, interstitial pulmonary fibrosis, infections (infectious mononucleosis, hepatitis B, tuberculosis, leprosy, syphilis, kala-azar, visceral leishmaniasis, schistosomiasis, malaria), infective endocarditis, IV drug abuse, following vaccination, transfusion, severe acute infections (transient)

Radiological changes

- Early radiological changes of the hands: marginal erosions, periarticular osteopenia
- Late radiological changes of the hands: diffuse osteoporosis, loss of cartilage, erosion and subluxation of MCP and PIP joints
Diagnostic/classification criteria for RA

1. Morning stiffness (≥ 1 h)
2. Swelling (soft tissue) of 3 or more joints
3. Swelling (soft tissue) of the hand joints (PIP, MCP, or wrist)
4. Symmetrical swelling (soft tissue)
5. Subcutaneous nodules
6. Serum RF
7. Erosions and/or periarticular osteopenia in hand or wrist joints seen on X-ray

4/7 must be present for diagnosis. Criteria 1-4 must be present for at least 6 weeks. Criteria 2-5 must be observed by a physician.

Diagnostic criteria of RA 2010

<table>
<thead>
<tr>
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<th>Score</th>
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<tbody>
<tr>
<td><strong>A. Joint involvement</strong></td>
<td></td>
</tr>
<tr>
<td>• 1 large joint</td>
<td>0</td>
</tr>
<tr>
<td>• 2-10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>• 1-3 small joints</td>
<td>2</td>
</tr>
<tr>
<td>• 4-10 small joints</td>
<td>3</td>
</tr>
<tr>
<td>• &gt; 10 joints (at least 1 small joint)</td>
<td>5</td>
</tr>
<tr>
<td><strong>B. Serology</strong></td>
<td></td>
</tr>
<tr>
<td>• RF and anti-CCP are negative</td>
<td>0</td>
</tr>
<tr>
<td>• RF or anti-CCP are positive in low titer</td>
<td>2</td>
</tr>
<tr>
<td>• Anti-CCP positive in high titer</td>
<td>3</td>
</tr>
<tr>
<td><strong>C. Acute phase reactants</strong></td>
<td></td>
</tr>
<tr>
<td>• Normal CRP and ESR</td>
<td>0</td>
</tr>
<tr>
<td>• Elevated CRP o ESR</td>
<td>1</td>
</tr>
<tr>
<td><strong>D. Duration of symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>• &lt; 6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>• &gt; 6 weeks</td>
<td>1</td>
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</tbody>
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Evaluation: RA can be diagnosed if score sum is at least 6

The differential diagnosis of RA
Acute viral arthritis, bacterial endocarditis, acute rheumatic fever, serum sickness, sarcoidosis, SNSA group (Reiter’s syndrome, psoriatic arthritis, IBD, Whipple’s disease), polyssystemic autoimmune diseases (SLE, Sjögren’s syndrome, PSS, PM/DM), vasculitis syndromes, polymyalgia rheumatic, gout, pseudogout, amyloidosis, paraneoplastic syndromes, erosive osteoarthritis

Therapeutic goals in RA
- Relief of pain
- Reduction of inflammation
- Protection of articular structures
- Maintenance of function
- Control of systemic involvement

Management of RA
- Education of patient and family in order to become aware of impact and to make appropriate accommodation in lifestyle
- Physical therapy: rest, splinting, exercise, orthotic and assistive devices
- Medical treatment
• Reconstructive orthopedic surgery: arthroplasty, total joint replacement, arthroscopic synoviectomy
• Follow-up: DAS score

Medical treatment of RA

NSAIDs
• COX-1 inhibitors: indomethacin, diclofenac, piroxicam, ibuprofen, naproxen, flurbiprofen, nimesulide, meloxicam
• COX-2 inhibitors: celecoxib

Low dose oral glucocorticoids (prednisone, prednisolone, methylprednisolone) dexamethasone,

Intra-articular glucocorticoids (betamethasone, triamcinolone)

Disease-modifying antirheumatic drugs (DMARDs) Methotrexate (10-25 mg/wk, PO), sulfasalazine, D-penicillamine, chloroquine

TNF-α neutralizing agents: etanercept, infliximab

Immunosuppressive and cytostatic drugs: azathioprine, leflunamide, cyclosporine A, cyclophosphamide

Course and outcome of RA
• < 20% will have no evidence of disability
• 50% will have work disability within 10 years
• Median life expectancy is shortened by 3-7 years
• Mortality rate is increased by 2.5x
• Main causes of death: infections, GI bleeding