The form circle of rheumatic inflammatory systemic diseases includes a number of diseases, whose etiology is mostly unknown. Due to the fact that specific antibodies are often found, diseases such as rheumatoid arthritis are considered autoimmune diseases. Therefore, the diagnosis of antibodies plays a significant role in the diagnosis of rheumatic diseases. The following article features two diseases, rheumatoid arthritis and Still's disease, both from the rheumatic disease form circle.

Symptoms of Rheumatoid Arthritis

Definition of rheumatoid arthritis

Rheumatoid arthritis by definition belongs to the chronic inflammatory systemic diseases and proceeds progressively in stages.

The basis of the disease is an inflammation of the synovial membrane, i.e. the inner layer of the joint capsule. Attributed to synovitis, it can lead to secondary diseases such as arthritis, bursitis or tenosynovitis.
Additionally, as part of rheumatoid arthritis, extra-articular organ involvement may also occur.

**Note:** The disease occurs in stages.

### Epidemiology of rheumatoid arthritis

The prevalence of the disease in the adult population is approximately 1 %. Starting at the age of 55, this increases to about 2 %. Overall, the prevalence increases with age, with the peak incidence occurring between the ages of 55 – 75 years.

Significantly more women than men are affected by the disease: In this case, a ratio of 2:1, up to 3:1.

### Etiology of rheumatoid arthritis

The etiology of rheumatoid arthritis is unknown, as with most diseases of the rheumatic type. Currently, a deregulation of the immune system is being discussed, at the dissolution of which **genetic predisposition** plays a crucial role.

Thus, approximately 70 % of patients suffering from rheumatoid arthritis display having the **HLA-Antigen DR4/DRB1**.
In addition to genetic predisposition, influences of noxious substances at the time of an outbreak of rheumatoid arthritis are also currently being discussed. Recent studies show, for example, that the consumption of nicotine is directly related to the disease' outbreak. Furthermore, smokers exhibit a severe progression of the disease and respond poorly to therapy.

Pathophysiology of rheumatoid arthritis

In patients who have a genetic disposition (see above), unknown triggers cause an autoimmune reaction. As part of this autoimmune response, migration of inflammatory cells into the synovium occurs.

![Image]("Rheumatoid Arthritis as seen through a microscope" by KGH. License: CC BY-SA 3.0)

These cells include auto reactive T-lymphocytes, B-lymphocytes, dendritic cells, as well as plasma cells. The interaction of cells with each other, especially between the lymphocytes and the monocytes causes a production of pro-inflammatory cytokines of immunoglobulins, as well as antibodies that are characteristic of rheumatoid arthritis, against the Fc fragment of IgG.

Note: The antibodies against the Fc fragment of the IgG are also known as rheumatoid factors.

Through the production of the pro-inflammatory cytokines certain signaling cascades are in turn set in motion, in the course of which an activation of the complement pathway and the release of other inflammatory mediators and enzymes is caused.

The released enzymes, such as collagenase or elastase, attack the cartilage. In addition, a destruction of the cartilage through a so-called pannus formation occurs. The pannus, which refers to a thickening of the synovial fluid, is caused on one hand by an invasion of macrophage-like cells and, on the other, through the proliferation of fibroblast-like cells.

Classification of rheumatoid arthritis

To provide an early diagnosis of rheumatoid arthritis, that is as reliable as possible, the ACR/EULAR classification criteria (2010) was developed.

As a prerequisite to gathering the classification criteria for the diagnosis, a sample of synovitis is required from at least one preferred joint. In addition, this synovitis should show no other discernible underlying causes; such as trauma or degenerative joint
The classification criteria are composed of clinical factors such as the progression (< 6 weeks, > 6 weeks) or the number of swollen and painful joints, as well as laboratory parameters, such as the presence of rheumatoid factors, anti-CCP antibodies or elevated CRP- or ESR values.

In each case, points from 0 to 6 are assigned per column, whereby only the highest score per column is counted. If the total score amounts to at least 6 points, the presence of rheumatoid arthritis can be expected.

**Note:** With the presence of at least 6 points as well as a secured synovitis (without any other apparent cause) the diagnosis of rheumatoid arthritis is made.

### Clinical signs of rheumatoid arthritis

Clinical signs of rheumatoid arthritis can be subdivided into non-specific general symptoms, specific symptoms, facultative symptoms as well as extra-articular organ manifestations.

#### Non-specific general symptoms in the context of rheumatoid arthritis

Typical general symptoms that can occur in the context of rheumatoid arthritis, including night sweats, a possible low-grade fever, myalgia, and a sense of fatigue.

#### Specific symptoms in the context of rheumatoid arthritis

Specific symptoms of rheumatoid arthritis include especially the symptoms of **polyarthritis**, **tenosynovitis** and **bursitis**.

These three symptoms usually occur symmetrically, the small joints on the fingers are most often affected at onset. On the fingers, the inflammation shows especially in the swelling of the proximal interphalangeal joints and the finger bases (= MCP and PIP joints).

**Note:** The finger base joints (DIP joints) are not usually affected.
The swelling is also painful, and we speak about the so-called **Gaenslen sign**, which occurs during a painful handshake.

More specific early symptoms of the disease are morning stiffness of the joints (> 30 minutes) and circulatory disorder of individual fingers.

A synovitis of the tendon sheaths in the area of the **transverse carpal ligament**, may lead to a compression of the extending **median nerve**. The resulting disease pattern, with paresthesia in the supply area of the nerves among others, is called **carpal tunnel syndrome**.
**Note:** Paresthesias in the context of carpal tunnel syndrome occurs mostly at night and during dorsiflexion of the hand.

**Optional symptoms in the context of rheumatoid arthritis**

In about 20% of cases, the appearance of the so-called *rheumatoid nodules* is present, which are mainly located in the tendons on the extensor surfaces of the joints and are located subcutaneously. The *elbow joint* is affected more frequently.

In about 30% of cases, a **secondary sicca syndrome** is present, which leads to decreased tear and saliva production, caused by inflammation of the respective gland. The sicca syndrome is also attributed to extra-articular organ manifestations (see below).

Additionally, it can possibly lead to nail changes, such as reddish crescents or subungual hemorrhages and nail growth disorders.

**Extra articular organ manifestations in the context of rheumatoid arthritis**

Among the organs that can be affected in the context of rheumatoid arthritis include: the *lungs*, the *liver*, eyes, as well as *blood vessels*. 
In approximately 50% of patients, the organ that is most affected is the lung. However, lung involvement, usually in the form of pleurisy, often remains asymptomatic. In rare cases, pulmonary fibrosis may occur.

Manifestation in the form of a peri- or myocarditis can occur in the heart. This affects approximately 30% of patients, which usually present as asymptomatic.

In connection with the liver, usually only an unspecific elevation of liver enzymes and rarely, a periportal fibrosis is found.

Renal involvement occurs rarely and usually appears in form of focal membranous glomerulonephritis, which is secondarily caused by the medical treatment of rheumatoid arthritis.

It can lead to vasculitis of the vessels, which may cause premature atherosclerosis or polyneuropathy among others. Due to these two factors, vasculitis is associated with a significantly increased cardiovascular risk.

Note: As part of the increased cardiovascular risk, affected patients are significantly more likely to suffer from a stroke or a heart attack.

Manifestation of the eye was already discussed under secondary sicca syndrome (keratoconjunctivitis sicca, see above).

Diagnosis of rheumatoid arthritis

In addition to the above-mentioned ACR/EULAR classification criteria for the early diagnosis of rheumatoid arthritis, clinical examination signs, laboratory parameters and a diagnostic apparatus are also involved in the diagnosis.

Clinical examination indications in the context of rheumatoid arthritis

In addition to the above-mentioned Gaenslen sign, as well as abnormalities in the hands, other signs can raise suspicion of possible rheumatoid arthritis.

These include, for example, skin folds that have spread past the metacarpophalangeal joints through swelling, or an atrophy in the musculi interossei (Dorsal interossei muscles of the hand).

Laboratory parameters in the context of rheumatoid arthritis

Non-specific signs of infection include an increase of ESR, CRP, as well as acute phase proteins, such as ferritin.

Other immunological findings represent the detection of rheumatoid factors or anti-CCP. Rheumatoid factors (see above) are positive at the beginning in about 40% of cases, and about 80% during progression of the disease. These are however not specific for rheumatoid arthritis, but may also be present in the context of chronic infectious diseases, liver diseases, or in healthy individuals (around 5%).

Compared with this, the anti-CCP, which represents an IgG-antibody to cyclic peptide citrulliertes, exhibits a high specificity (> 90%). In addition, the anti-CCP, in conjunction with a positive rheumatoid factor, provides an indication of an aggressive progression of rheumatoid arthritis.

In 30% of cases antinuclear antibodies (ANA) can also be detected.

Instrumental diagnostics in the context of rheumatoid arthritis
As part of an apparative diagnosis, sonography and conventional X-rays are used.

By means of a sonographic examination for example, a joint effusion, evidence of a Baker’s cyst, a hyper perfusion of the **synovium** (via PW Doppler) or pannus can be indicative of rheumatoid arthritis.

The findings upon examining an X-ray are classified according to **Steinbrocker** in 0 – IV stages. In stage 0 no clinical signs of disease nor striking radiographic findings can be reported. In stage I, X-rays already show first soft tissue characters and a possible **juxtaarticular osteoporosis**.

In stage II, incipient cartilage and bone destruction are described as well, and in stage III incipient subluxations and misalignments are added. Due to these effects, the joint mobility is already severely limited in stage III, whereas it only interferes slightly in stage II and does not interfere at all in stage I + O, meaning, it is fully maintained.

In stage IV, joint mobility is no longer possible due to the existence of joint destruction and complete dislocations or **ankylosis**.

**Note:** Since radiographic changes often only occur in the later course of the disease, the absence of changes on the X-ray does not exclude rheumatoid arthritis. Other apparatus that can be used for examination are MRI, contrast-enhanced MRI, scintigraphy and a joint puncture combined with examination of the synovial fluid.

**Special Forms of Rheumatoid Arthritis**

The special forms of rheumatoid arthritis include the Caplan- and Felty’s syndrome, **juvenile idiopathic arthritis** and **age-rheumatoid arthritis**.

The **Caplan’s syndrome** represents a combination of rheumatoid arthritis and silicosis and occurs mainly in miners.

The Felty’s syndrome, however, describes a severe form of rheumatoid arthritis, which can cause symptoms such as **hepatosplenomegaly**, **lymphadenopathy** and **granulocytopenia** during adulthood.

Rheumatoid arthritis beginning after age 60 is called age-RA, whereas **juvenile idiopathic arthritis** manifests before the age of 16. **Juvenile idiopathic arthritis** can be further divided into sub-categories, including systemic arthritis (synonym: Still’s disease (see below) among others).

**Note:** Age-RA often shows an aggressive progression accompanied by early joint destruction.
Differential diagnosis (DD) of rheumatoid arthritis

Differential diagnosis of rheumatoid arthritis roughly includes the other diseases of the rheumatic type. These include, for example, **psoriatic arthritis**, connective tissue diseases, such as **systemic lupus erythematosus**, or **vasculitis**.

However, other systemic diseases, such as hemochromatosis, gout or rheumatic fever, which can also lead to joint participation, should be considered during differential diagnosis.

Another important differential diagnosis is osteoarthritis.

Treatment of rheumatoid arthritis

**Physical therapy of rheumatoid arthritis**

A pillar of the treatment of rheumatoid arthritis is physical therapy. This includes especially cooling applications in the form of cryotherapy during acute episodes. In addition to cryotherapy, thermo-, hydro-, electro- as well as exercise and massage therapy are used.

**Note:** In acutely inflamed joints do not apply heat, only cryotherapy.

**Drug treatment of rheumatoid arthritis**

In connection with the treatment of rheumatoid arthritis is the guiding principle that, as soon as the diagnosis is made, therapy with classical DMARDs (disease-modifying anti-rheumatic drugs) should be initiated, since this can lead to rapid remission and low disease activity.

Classic DMARDS include for example MTX (**methotrexate**), which should initially be used in active rheumatoid arthritis. If well tolerated, or combined with lack of efficacy, the dose may be increased or the first oral dose be converted to a parenteral one.

In connection with the administration of MTX, which is a folic acid antagonist, side effects should be paid attention to, which may occur especially gastro-intestinally, e.g. in the form of nausea. Other side effects include, stomatitis, an increase in liver enzymes and cytopenia due to a depression of the bone marrow.

**Note:** MTX is a folic acid antagonist with an immunosuppressive effect. Delayed delivery of folic acid (approximately 24 – 48 hours after MTX intake) can reduce the incidence of side effects.

Because of the delayed onset of MTX (after weeks - months), an initial low to medium dose of glucocorticoids should be given as a supplement. This principle also applies to the other DMARDs, because they also have a delayed onset of action.

**Note:** Glucocorticoids do not only have an anti-inflammatory, but also a disease modifying effect, resulting to a combination with DMARDs having a positive effect on disease progression.

If MTX is out of the question as a primary DMARD, or therapy is causing severe side-effects (see above), another classic DMARD should be used. These include for example, leflunomide, sulfasalazine, antimalarial preparations such as hydroxychloroquine, other immunosuppressant’s such as cyclosporine A or azathioprine, or alkylating agents such as cyclophosphamide.

**Note:** For the administration of cyclosporin A and cyclophosphamide their toxicity must
be considered, therefore, cyclophosphamide should only be used in exceptional cases. Other drugs in the treatment of rheumatoid arthritis are biologicals. Biologicals, which represent recombinantly produced antibodies, include antibodies against tumor necrosis factor-α (infliximab, adalimumab, Entanercept, golimumab, certolizumab), anti-CD-20-AK (rituximab) and interleukin-1 receptor antagonists (anakinra).

Because an initial combination of different DMARDs has shown no greater effectiveness in studies, monotherapy should initially be sought (initially in combination with glucocorticoids). This means, if a therapy with MTX is not successful initially, another DMARD can be used.

If the primary goal of therapy, meaning remission or low disease activity, is not reached through monotherapy, a combination of several DMARDs should follow. In a disease with currently high activity, a combination with a biological can be considered. Primarily, MTX should be combined with a biological.

Otherwise, biologicals are mostly used when the combination of two DMARDs has not achieved a sufficient therapeutic effect.

**Interventional therapy of rheumatoid arthritis**

This includes procedures such as radio-synoviorthesis, synovectomy (arthroscopy or surgical) as well as reconstructive surgery.

As part of radio-synoviorthesis, radioactive substances (beta emitters) are injected into the inflamed joint. Via this treatment, the joints become pain-free in the long-term, with the optimum onset of effect occurring after 3 - 6 months.

**Complications of rheumatoid arthritis**

The disease itself may lead to a number of irreversible changes in the joints. Deformities of the hands are especially common, as these are often affected early in the disease process.

These include e.g. the swan neck deformity of the fingers or boutonniere deformity of the proximal interphalangeal joints. The swan neck deformity causes hyperextension in the proximal interphalangeal joint and flexion in the distal interphalangeal joint.

The boutonniere deformity however causes the central joints to be in a flexed position and the distal interphalangeal joints to be hyperextended.
Besides the two mentioned deformities, it can also lead to an ulnar deviation of the fingers.

In the area of the cervical spine, atlanto axial subluxation can occur. This poses the risk of paraplegia.

In addition to the joint changes described above, it can also lead to complications in connection with the extra-articular organ involvement. These include coronary heart disease (CHD) and premature atherosclerosis.

Additionally, it may lead to the occurrence of amyloidosis type AA, among others. This leads to an accumulation of the precursor protein of amyloid, the serum amyloid A. An accumulation usually occurs in the kidneys, the liver, the spleen, the adrenal glands, and the gastrointestinal tract.

The accumulation in the kidney area can lead to nephrotic syndrome and renal failure as a consequence.

In addition, complications of drug therapy can result from the side effects of the therapeutic agents used. An incidence of gastric and duodenal ulcers, as well as bleeding often occurs, especially during the administration of NSAIDs.

The administration of immunosuppressant's may further lead to infections, or as part of glucocorticoid administration, to osteoporosis, among others.

**Prognosis of rheumatoid arthritis**

Overall, the disease progression is very unique depending on the individual. Further progression is especially difficult to estimate at the beginning of the disease. However, there are certain factors that are associated with poor prognosis.

These include, for example, laboratory parameters such as elevated CRP or elevated ESR values, the detection of anti-CCP antibodies and an increased rheumatoid factor titer.

Due to the fact that early treatment has a positive effect on the prognosis, certain factors that are associated with a poorer response to treatment, are to be regarded as prognostically unfavourable. These include e.g. high disease activity, female gender, smoking as well as four genetic polymorphisms.
Clinical Picture of Still’s Disease

Definition of Still’s disease

Morbus Still or Still’s disease is part of rheumatic disorders. Whereas its etiology is unknown, a distinction should be made between Juvenile Still’s disease, which is a subtype of juvenile idiopathic arthritis, and Adults Still’s disease.

Epidemiology of Still’s disease

Adult Still’s disease is an extremely rare disease (incidence rate is about 5/100,000), men and women are equally affected.

Juvenile Still’s disease begins at infancy.

Clinical symptoms of Still’s disease

The characteristic feature of the adult, as well as the juvenile Still’s disease is a speckled, salmon-coloured, maculopapular rash, which occurs only fleetingly and spreads to the trunk and proximal extremities.

**Note:** Due to the fact that the rash occurs only fleetingly and often in conjunction with nightly fevers, it is rarely present when patients visit a doctor.

Other symptoms associated with Still’s disease are fevers (> 39 °C) that occur 1 – 2 times per day and in some cases are associated with intense muscle and joint pain.

Arthritis of the joints, compared with rheumatoid arthritis, represents polyarthritis, i.e. several joints are affected. The distribution is, similar to that of rheumatoid arthritis, symmetrically pronounced.

**Note:** Joint involvement in the juvenile forms in the background initially.

Other optional symptoms are a sore throat, splenomegaly and polyserositis of the pleura and pericardium.

Diagnosis of Still’s disease

First is the exclusion of other causes, such as infections or neoplasia. For further diagnostics the so-called major and minor criteria according to Yamaguchi exist. For diagnosis, a total of five criteria have to be met, of which at least two must be in the major criteria.

Major criteria according to Yamaguchi:

- Intermittent fever (> 39 °C) for a minimum period of one week
- Arthralgia for at least two weeks
- Representation of the typical rash
- Leukocytosis > 10,000 / μl with neutrophilia

Minor criteria according to Yamaguchi:

- Sore throat
- Lymphadenopathy and/or splenomegaly
- Elevated liver enzymes
- Negative rheumatoid factor and negative ANAs
Therapy of Still’s disease

The treatments of choice are corticosteroids, possibly in combination with MTX.

Another option is other immunosuppressant’s, or biologicals such as IL-1 receptor antagonists, TNF-α antibodies and intravenous immunoglobulins.

Complications of Still’s disease

Possible complications of Still’s disease are hemophagocytosis, an activation of the coagulation system, as well as multi-organ failure.

A specific complication in this context is the macrophage activation syndrome, which is accompanied by an uncontrolled activation of macrophages and a massive release of cytokines.

Review Questions

The answers can be found below the references.

1. Which statement about rheumatoid arthritis is not true?
   A. Rheumatoid arthritis is one of the autoimmune diseases.
   B. Progression occurs in stages.
   C. A symmetrical polyarthritis is present, which affects especially the finger bases and proximal interphalangeal joints of the hand.
   D. Extra-articular organ manifestation may occur.
   E. Rheumatoid factors represent antibodies against the Fc fragment of IgA.

2. Which statement about the special forms of rheumatoid arthritis is true?
   A. The Caplan syndrome refers to the combination of rheumatoid arthritis and asbestosis.
   B. A milder disease progression is to be expected for the Felty syndrome.
   C. Age-RA begins after age 60, and is often distinguished by a more aggressive disease progression.
   D. Juvenile idiopathic arthritis occurs before age 5.
   E. Still’s disease is associated with Age-RA.

3. Which statement about Still’s disease is correct?
   A. A fleetingly occurring, salmon-coloured macopapular rash is characteristic of Still’s disease.
   B. Symptoms include asymmetric oligoarthritis.
   C. Rheumatoid factors are typically positive.
   D. ANAs are typically positive.
   E. Onset of the juvenile form usually occurs after the age of 16.

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**Correct answers:** 1E, 2C, 3A

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