Rheumatoid Arthritis (RA, Atrophic Arthritis) and Still’s Disease — Symptoms and Treatments

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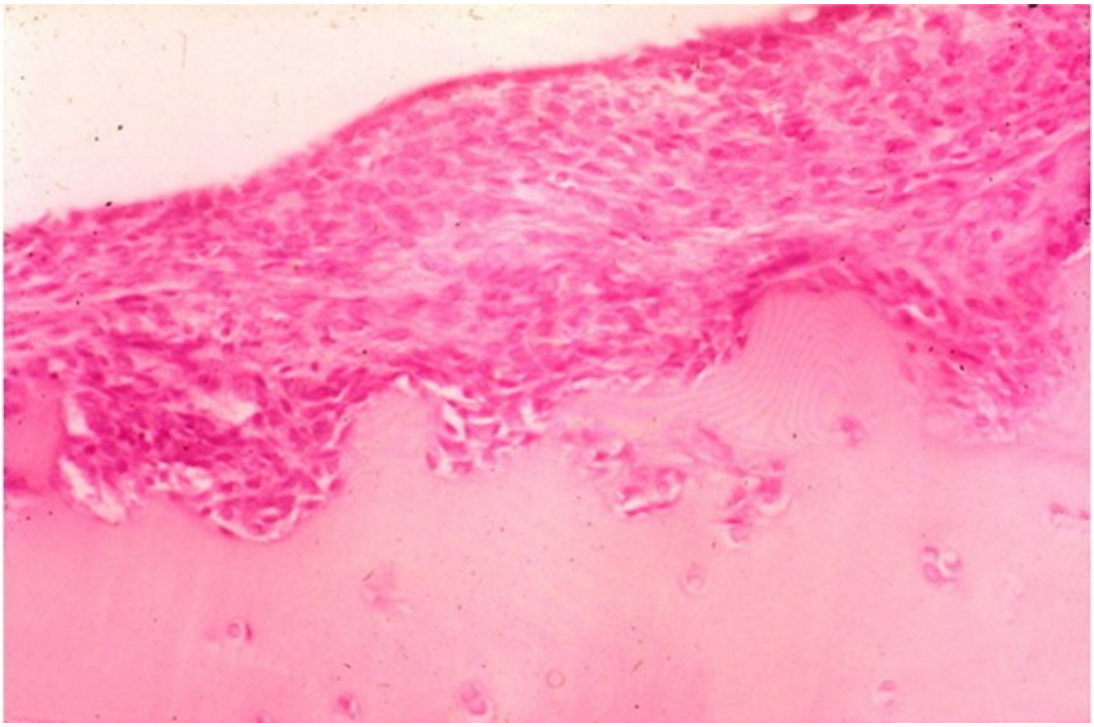
The group of Rheumatic inflammatory systemic diseases includes several diseases, whose etiology is mostly unknown. Since specific antibodies are often found, diseases such as rheumatoid arthritis are considered autoimmune diseases. Therefore, the diagnosis of antibodies plays a significant role in the diagnosis of rheumatic diseases. The following article features 2 diseases from this group of rheumatic diseases: Rheumatoid arthritis and Still's disease.



Definition of Rheumatoid Arthritis

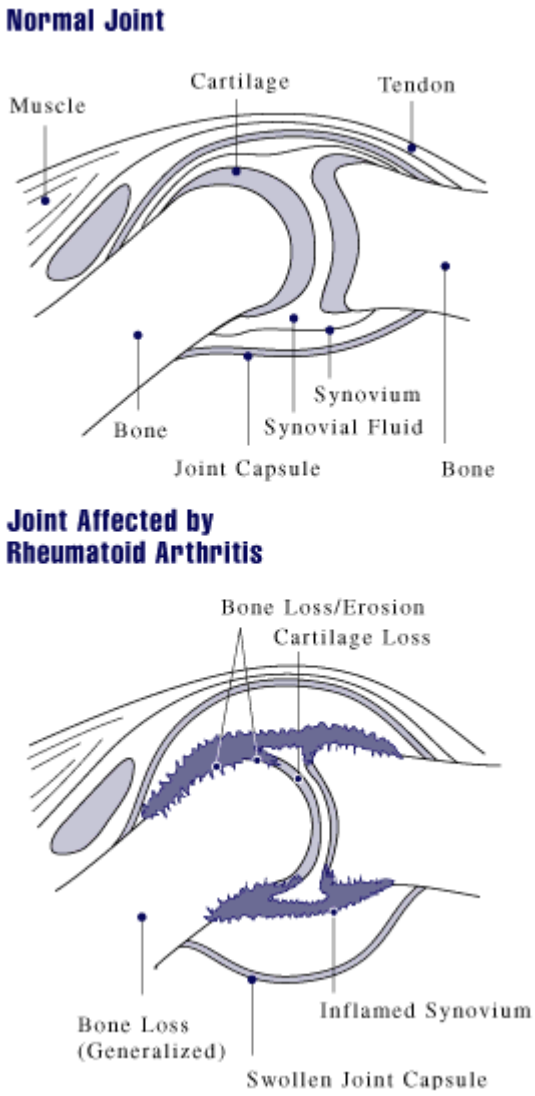


Image: Reumathoide arthritis changes on the joint. By US gov, License: Public domain

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.**

The disease causes polyarticular, symmetrical arthritis with extra-articular manifestations:

- Rheumatoid nodules (skin, lungs); rheumatoid lung (interstitial fibrosis); rheumatoid vasculitis (skin, nerve, internal organs)
- Episcleritis/scleritis
- Felty's syndrome
- Pericarditis

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 approx. 1%. Starting at age 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 with 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, dysregulation of the immune system is being discussed as a possible cause, at the dissolution of which genetic predisposition plays a crucial role.

Thus, approx. 70% of patients who have rheumatoid arthritis display the **HLA antigen DR4/DRB1**.

In addition to genetic predisposition, the influence 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 predisposition (see above), unknown triggers cause an autoimmune reaction. As part of this autoimmune response, migration of inflammatory cells into the **synovium** occurs.

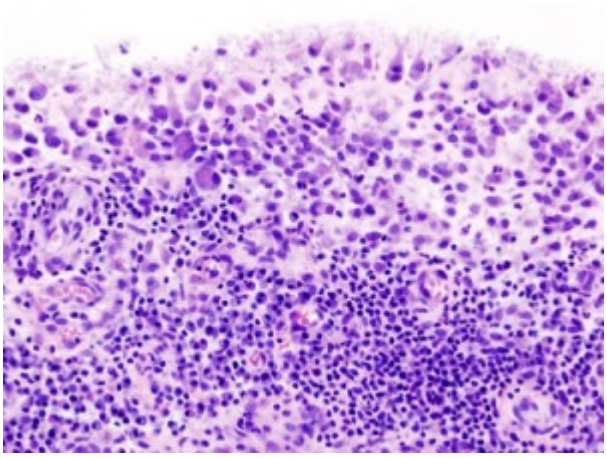


Image: Rheumatoid Arthritis as seen through a microscope. By KGH, License: CC BY-SA 3.0

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

Note: The antibodies against the Fc fragment of 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 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, the 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. Also, this synovitis sample should show no other discernible underlying causes, such as trauma or degenerative joint changes of other origins.

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 factor, anti-CCP antibodies, elevated C-reactive protein (CRP) value, or elevated erythrocyte sedimentation rate (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.

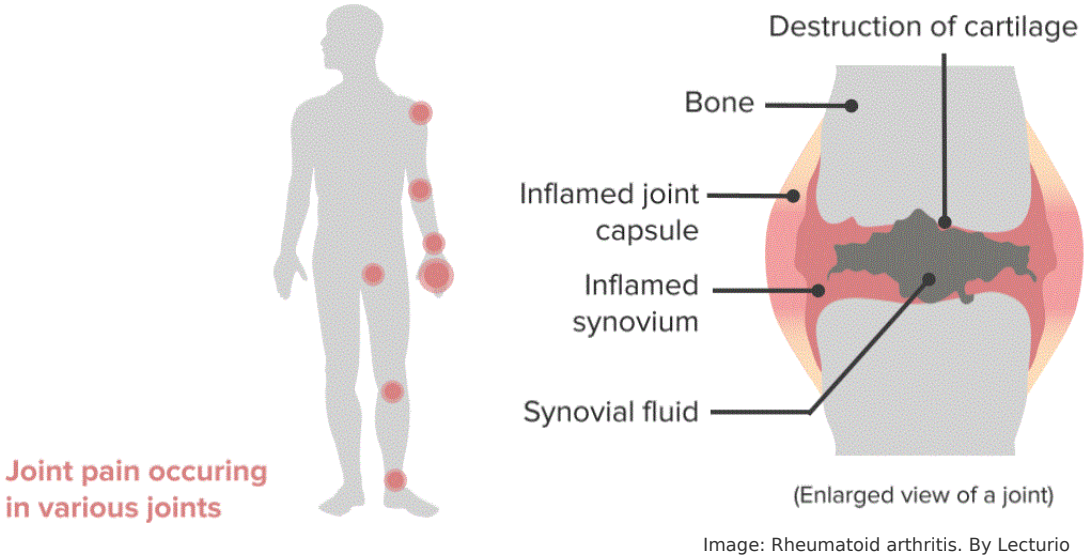


Image: Rheumatoid arthritis. By Lecturio

Note: The diagnosis of rheumatoid arthritis can be confirmed by the presence of at least 6 points as well as securing a synovitis sample that indicates no other apparent cause.

Clinical Signs of Rheumatoid Arthritis

Clinical signs of rheumatoid arthritis can be subdivided into nonspecific general

symptoms, specific symptoms, facultative symptoms, as well as extra-articular organ manifestations.

Nonspecific general symptoms in the context of rheumatoid arthritis

Typical general symptoms that can occur in the context of rheumatoid arthritis include 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 **polyarthritis, tenosynovitis,** and **bursitis.**

These 3 symptoms usually occur symmetrically. The small joints on the fingers are most often affected at the onset. On the fingers, the inflammation shows, especially in the swelling of the proximal interphalangeal (PIP) joints and the finger bases.

Note: The finger base joints (distal interphalangeal joints) are usually not affected.
The other symptoms include 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.

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, is called **carpal tunnel syndrome**.

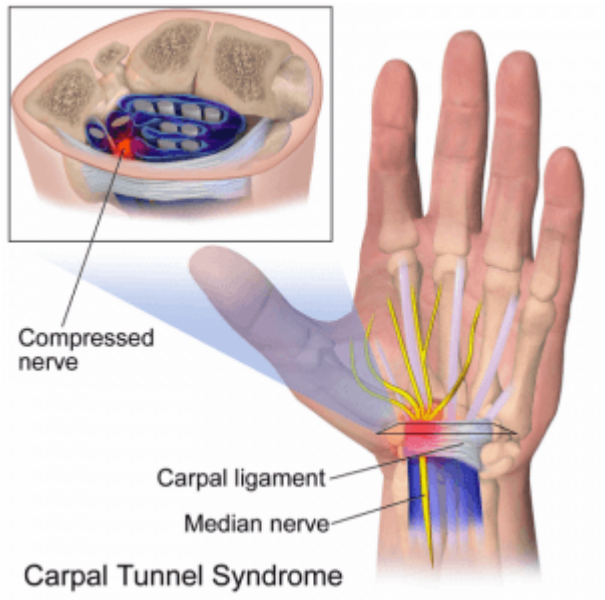


Image: Carpal tunnel syndrome. By Bruce Blaus, License: CC BY 3.0

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 so-called **rheumatoid nodules** appear mainly in the tendons on the extensor surfaces of the joints and subcutaneously. The elbow joint is affected more frequently.

Image: Rheumatoid arthritis. By Godart, Thomas, License: CC BY 4.0

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 glands. 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 heart, the lungs, the liver, eyes, as well as blood vessels.

In approx. 50% of patients, the lung is the most affected organ. However, lung involvement, usually in the form of pleurisy, often remains asymptomatic. In rare cases, **pulmonary fibrosis** may occur.

Manifestation in the form of **pericarditis** or **myocarditis** can occur in the heart. It affects approx. 30% of patients who usually present as asymptomatic.

About the liver, an unspecific elevation of liver enzymes is usually observed. However, **periportal fibrosis** is found rarely.

Renal involvement rarely occurs and usually appears in the 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 2 factors, vasculitis is associated with 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.
The manifestation of the eye was already discussed under secondary sicca syndrome (**keratoconjunctivitis sicca**, see above).

Diagnosis of Rheumatoid Arthritis

In addition to the ACR/EULAR classification criteria mentioned above, the early diagnosis of rheumatoid arthritis involves clinical examination signs, laboratory parameters, and a diagnostic apparatus.

Clinical examination indications in the context of rheumatoid arthritis

In addition to the Gaenslen sign mentioned above, 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 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 that indicate rheumatoid arthritis include 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 the 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 the anti-CCP, the IgG antibody to cyclic citrullinated peptide exhibits a high specificity (> 90%). In addition, the anti-CCP, in conjunction with a positive rheumatoid factor, indicates an aggressive progression of rheumatoid arthritis.

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

Target population: Patients who have at least 1 joint with clinical synovitis and with the synovitis not explained by another disease.

		Score
A. Joint involvement (tender/swollen)	1 large joint	0
	2–10 large joints	1
	1–3 small joints	2
	4–10 small joints	3
	> 10 joints (at least 1 small joint)	5
B. Serology	Negative RF & ACPA	0
	Low-positive RF/low-positive ACPA	2
	High-positive RF/high-positive ACPA	3
C. Acute-phase reactants	Normal CRP & ESR	0
	Abnormal CRP & ESR	1
D. Duration of symptoms	< 6 weeks	0
	> 6 weeks	2

Instrumental diagnostics in the context of rheumatoid arthritis

Diagnostic apparatus used to detect rheumatoid arthritis include sonography and conventional X-rays.

A sonographic examination can detect, for example, joint effusion, evidence of a Baker’s cyst, hyperperfusion of the **synovium** (via pulsed wave Doppler), or pannus, and these 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 soft tissue characteristics 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 + 0, 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**.

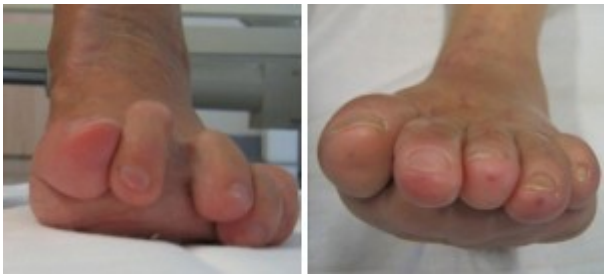


Image: a) Luxated toes at RA b) after Stainsby correction. By Angela Simon, License: CC BY-SA 3.0

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 Caplan's syndrome, Felty's syndrome, **juvenile idiopathic arthritis,** and **age-rheumatoid arthritis**.

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

Felty's syndrome 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 subcategories, including systemic-onset arthritis (also known as Still's disease), 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.**

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

Physical therapy is an essential pillar of rheumatoid arthritis treatment. Therapy includes cooling applications in the form of cryotherapy, especially during acute episodes. In addition to cryotherapy, thermo-, hydro-, electro-therapy 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

As soon as the rheumatic disease is diagnosed, therapy with classical DMARDs (disease-modifying antirheumatic 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 a lack of efficacy, the dose may be increased, or the 1st oral dose is 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 gastrointestinally, 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 (approx. 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 not only have an anti-inflammatory but also a disease-modifying effect, and in combination with DMARDs result in 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 immunosuppressants such as cyclosporin 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-alpha (infliximab, adalimumab, Etanercept, golimumab, certolizumab), anti-CD20 (rituximab), and interleukin-1 receptor antagonists (anakinra).

Since an initial combination of different DMARDs has shown no greater effectiveness in studies, monotherapy should be sought (initially in combination with glucocorticoids). Therefore, if 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 2 DMARDs has not achieved a sufficient therapeutic effect.

Interventional therapy of rheumatoid arthritis

Interventional therapy includes procedures such as **synoviorthesis, synovectomy** (arthroscopy or surgical), as well as **reconstructive surgery.**

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

Complications of rheumatoid arthritis

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

As the disease progresses, joint destruction occurs, resulting in deformity:

- Ulnar deviation of the fingers
- Swan-neck deformity of the fingers
- Boutonniere deformity of the fingers
- Atlantoaxial (C1-C2) subluxation may cause spinal cord injury in patients who have vertebral joint involvement

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**.

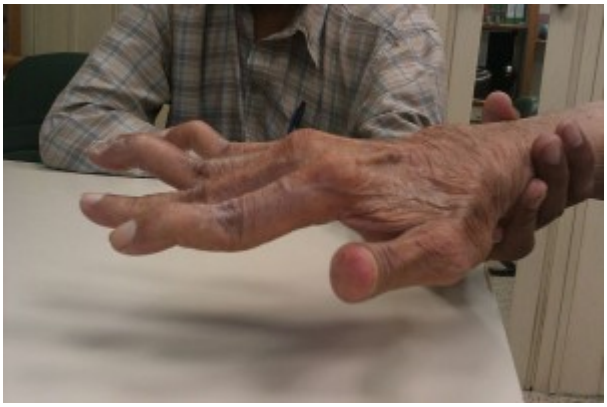


Image: Swan neck deformity in a 65-year-old rheumatoid arthritis patient. By Phoenix, License: CC BY-SA 3.0

The boutonniere deformity, however, causes the central joints to be in a flexed position and the **distal interphalangeal joints** to be hyperextended.

Besides the 2 mentioned deformities, it can also lead to ulnar deviation of the fingers.

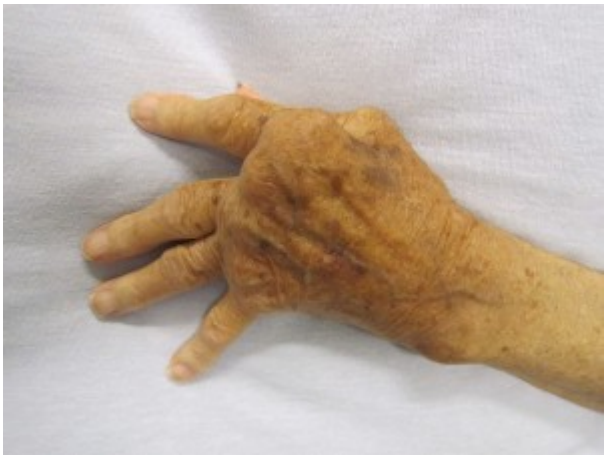


Image: Ulnar deviation of the fingers. By James Heilman, License: CC BY-SA 3.0

In the area of the **cervical spine**, **atlantoaxial subluxation** can occur, which 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, which in turn 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 nonsteroidal anti-inflammatory drugs (NSAIDs).

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

Prognosis of rheumatoid arthritis

Overall, disease progression is unique to the individual. Further progression is especially difficult to estimate at the beginning of the disease. However, certain factors 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.

Since 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 unfavorable. These include, e.g., high disease activity, female gender, smoking, as well as 4 genetic polymorphisms.

Clinical Picture of Still’s Disease

Definition of Still’s disease

Still’s disease is a type of rheumatic disorder. It is of unknown etiology. A distinction should be made between juvenile Still’s disease, which is a subtype of **juvenile idiopathic arthritis**, and adult-onset Still’s disease.

Epidemiology of Still’s disease

Adult-onset Still’s disease is extremely rare (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-colored, maculopapular rash, which occurs only fleetingly and spreads to the trunk and proximal extremities.

Note: Since 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 (> 39.0°C/ 102.2°F) that occur 1–2 times per day and in some cases, intense muscle and joint pain.

Like rheumatoid arthritis, polyarthritis of the joints is associated with Still’s disease. The distribution is similar to that of rheumatoid arthritis, symmetrically pronounced.

Note: Joint involvement in the juvenile forms in the background initially.
Other symptoms are sore throat, splenomegaly, and polyserositis of the pleura and pericardium.

Diagnosis of Still’s disease

The 1st step in the diagnosis of Still’s disease involves excluding other causes, such as infections or neoplasia. For further diagnostics, **Yamaguchi’**s major and minor criteria exist. For diagnosis, a total of 5 criteria have to be met, of which at least 2 must be in the major criteria.

Major criteria according to Yamaguchi:

- Intermittent fever (> 39°C / 102.2°F) for a minimum period of 1 week
- Arthralgia for at least 2 weeks
- Representation of 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 immunosuppressants 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, 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 uncontrolled activation of macrophages and a massive release of cytokines.

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Notes