
A systematic comparison of rheumatoid arthritis and ankylosing spondylitis

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Received and accepted on July 29, 2009.

Clin Exp Rheumatol 2009; 27 (Suppl. 55):
S43-S49.

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EXPERIMENTAL RHEUMATOLOGY 2009.

Key words: Rheumatoid
arthritis, ankylosing spondylitis,
clinical symptoms.

ABSTRACT

The clinical manifestations of rheumatoid arthritis (RA) and ankylosing spondylitis (AS) differ in many ways. The age of onset in AS is much younger, with an average onset of 28 years compared with 40–50 years in RA, and with a male predominance (3:1) compared with the female predominance in RA. The genetic association with HLA alleles is stronger in AS, with an HLA-B27 antigen in 95% of the patients compared with RA, with 60% HLA DR4 or DR1 positives. The type and localisation of arthritis is peripheral polyarthritis in RA, especially with involvement of hands and feet, whereas in AS the arthritis is mainly localized in the spine and sacroiliac joints with an oligoarthritis of the larger joints (hips, knees, shoulders). The radiographic signs in RA show bone resorption with erosive changes in contrast with AS where bone formation with vertebral syndesmophytes is present. Extra-articular manifestations can occur in both diseases but again these manifestations differ in the eye (keratoconjunctivitis sicca and scleritis in RA, versus anterior uveitis in AS), heart (pericarditis in RA, conduction disturbances in AS), lungs (pleural lesions or nodules in RA and fibrosis in AS) and gastrointestinal tract (peptic ulcers in RA and colitis in AS). Both diseases respond well to treatment with NSAIDs but DMARDs, which are very important in RA, have limited value in AS. TNF alpha blocking drugs, however, show a high efficacy in both diseases.

Definition of the diseases

Rheumatoid arthritis has a prevalence of 1–2% in the Caucasian population (Table I) and is characterised by polyarthritis, especially of the small joints of hands and feet.

The diagnosis is made on clinical judgement of the rheumatologists. The most

often used classification criteria are the 1987 American Rheumatism Association (ACR criteria) (1) which include symmetrical polyarthritis, involvement of the hand joints, rheumatoid nodules, radiographic erosions and the presence of the rheumatoid factor. Unfortunately the ACR-criteria lack sensitivity early in the disease (2).

Ankylosing spondylitis (AS) has a prevalence up to 0.9% in the Caucasian population (3) (Table I) and presents with low back pain and morning stiffness due to a chronic inflammation of the sacroiliac (SI) joints and vertebral column. The diagnosis of definite AS requires fulfilment of the modified New York criteria (4): obligatory are signs of a bilateral sacroiliitis grade 2–4 or unilateral sacroiliitis grade 3 or 4 at the x-ray of the pelvis (Fig. 3) plus at least one criterion out of 3 (inflammatory back pain, limited lumbar spinal motion in sagittal and frontal planes and decreased chest expansion relative to normal).

Etiology

RA as well as AS have a multifactorial cause, but genetic influences play a major role in both diseases. In RA, specific Human Leukocyte Antigen (HLA) class II genes at HLA-DR4 (DRB1*0404 and 0401) and DR1 (DRB1*1001), are present in 60% of the patients. In AS, the main genetic component is localized at an HLA class I gene, HLA-B27 (5), which is present in 95% of the patients (Table I).

The age at onset differs between RA and AS, because the first symptoms of AS most often starts at an earlier age compared with RA. RA can start at any age, but there is a peak incidence between 40–70 years of age. In contrast, AS most often begins in late adolescence or early adulthood with an average age of onset at 28 years (6). The onset of complaints in AS is often gradual and

Competing interests: none declared.

the mean delay is 8 years to the time of diagnosis (7).

The male: female ratio in RA is 1: 2-4, which is in contrast with AS which afflicts males 3 times more often than females (8) (Table I).

In RA, pregnancy seems to have a positive influence on both delaying the disease onset and decreasing disease activity during pregnancy itself (9).

In AS however, pregnancy was reported as a precipitating factor for AS and disease activity improved in only 30% of the patients during pregnancy (10).

Clinical symptoms

Arthritis

RA is characterized by symmetrical pain and swelling of the proximal interphalangeal (PIP) and metacarpal joints (MCP) of the hands and the metatarsal joints (MTP) of the feet. Arthritis also occurs in the wrists, elbows, shoulders, knees, hips, ankles, etc. The onset of the disease can start with an mono- or oligoarticular pattern, but often progresses to a polyarticular form. The clinical symptoms include pain and swelling of the joints, morning stiffness, lasting more than one hour, and fatigue.

In AS, peripheral arthritis occurs in approximately one third of the patients, especially in the knees, hips and shoulders (11) and shows an asymmetrical pattern. Hip involvement is usually bilateral, and can lead to destruction which might make total joint replacement necessary at a relatively young age (12). Arthritis of other peripheral joints like wrists, elbows, hands and feet occur as well. Typical for AS, in contrast with RA, is the occurrence of dactylitis, a sausage like swelling of a finger or toe.

Spinal features

In RA, the cervical spine can be involved, particularly at C1-C2-level, in very severe, long standing, erosive disease, with pannus formation and compression of the spinal cord.

The spinal involvement in AS results in complaints of chronic inflammatory back pain with morning stiffness. This morning stiffness lasts typically one hour or more, improves with exercise but is not relieved by rest. The low

Table I. Differences in clinical picture of rheumatoid arthritis and ankylosing spondylitis.

	Rheumatoid arthritis	Ankylosing spondylitis
<i>Etiology</i>		
Genetic association	HLA-DR4 and DR1	HLA-B27
male : female ratio	1:2-4	3:1
Peak incidence	40-70 years	20-45 years
Prevalence	1-2%	0.2-0.9%
<i>Clinical pattern</i>		
Predominant localization arthritis	hands and feet: MCP, PIP, MTP joints	sacroiliac joints knees, hips, shoulders
Arthritis pattern	symmetrical	asymmetrical
Number of joints	polyarthritis	oligo-arthritis
Enthesitis	-	+ especially Achillestendon
Spine involvement	- sometimes cervical spine	+ whole spine
<i>Laboratory tests</i>		
Increased ESR or CRP	majority in active disease	only 50-60% in active disease
Rheumatoid factor and/or anti-CCP	+ in 60-70%	-
<i>Radiographic signs</i>		
Sacroiliitis	-	+
Radiographic signs	bone resorption (erosions)	bone formation (syndesmophytes)

+ = present; - = absent.

back pain is caused by inflammation of the sacroiliac (SI) joints and vertebral column. Pain of the thoracic spine, especially with chest expansion, can be caused by involvement of the cervical and costovertebral joints.

The spinal inflammation can lead to ankylosis with a limited chest expansion, limited neck motion, thoracic kyphosis and flattening of the lumbar spine. These deformities, which often evolve after more than 10 years of the disease, result in a characteristic stooped forward posture and difficulties in looking forwards (13).

In a progressed disease, atlanto-axial subluxation might occur like in RA, due to erosions of the cervical structures (14).

Osteoporosis

Osteoporosis frequently occurs in RA as well as in AS. In RA it is related to higher age, the use of corticosteroids, and to the severity of RA, measured by high radiological damage (15). The number of vertebral and peripheral fractures is roughly doubled in RA patients (16).

In AS, osteoporosis is more common in patients with syndesmophytes, cervical fusion and peripheral joint involvement. In contrast to RA, most AS patients, show a decreased bone mineral density even after a short disease

duration. Moreover, in RA osteoporosis more often occurs among women, but in AS it occurs in young males (17).

AS patients, like in RA, also have an increased risk of vertebral fractures (Standard Morbidity ratio of 7.6), which seems to be related to a longer disease duration (18-20).

On the other hand, the risk of limb fractures, which is doubled in RA, is not significantly increased in association with AS (21).

Enthesitis

In AS, many patients suffer from pain due to enthesitis, an extra-articular bony tenderness caused by local inflammation. Many sites can be involved, like costosternal junctions, spinous processes, iliac crests, great trochanters, ischial tuberosities, tibial tubercles or more peripheral tendon insertions, like the Achilles tendons (22). In RA, enthesitis is a much less predominant feature but tendovaginitis is more common, especially of the wrists and hands.

Extra-articular features do occur in RA as well as in AS (Table II), and the most common sites for these features are the skin, the eye, heart, lungs and the gastrointestinal tract.

The skin

Psoriatic lesions of the skin occur more often in AS compared with RA. In con-

Table II. Differences in extra-articular manifestations between rheumatoid arthritis and ankylosing spondylitis.

	Rheumatoid arthritis	Ankylosing spondylitis
Skin	rheumatoid nodules	psoriasis (10%)
Eyes	keratoconjunctivitis sicca (10–15%)	acute anterior uveitis (30–40%)
Heart	pericarditis	AV-conduction disturbances, mitral valve insufficiency
Lungs	pleural lesions (lung nodules, interstitial lung disease)	apical fibrosis
Gastrointestinal tract	peptic ulcers	Colitis, ulcers (due to NSAIDs)
Blood vessels	vasculitis (<5%)	–

– = absent.

trast, subcutaneous rheumatoid nodules are typical for RA and do not occur in AS. Most often these painless, firm nodules occur in long standing, rheumatoid factor positive cases of RA at bony prominences, like the olecranon, finger joints, etc.

The eye

Acute anterior uveitis occurs in 30–40% of the AS patients, presenting with acute pain, loss of vision and redness of one eye which subsides spontaneously after several weeks. Rapid treatment by the ophthalmologist is required in order to prevent synechiae formation which finally might result in glaucoma and blindness.

In RA, keratoconjunctivitis sicca is more common. Local treatment with eye-drops does give some relief but many other therapeutic options are not available. In long standing RA this keratitis can be complicated by corneal melting with local perforation. Furthermore, a scleritis can occur as part of a rheumatoid vasculitis.

The heart

In RA, pericardial involvement was detected in ultrasound studies showing small pericardial effusions, while actual clinical manifestations of pericarditis are uncommon.

The risk at cardiovascular disease, however, is increased in RA as well as in AS and can be reduced by treating the inflammation adequately (23, 24).

Aortic valve incompetence can occur in long standing AS in 1–10% and involvement of the atrioventricular node is

possible, resulting in conduction disturbances in 1–33% (25). The latter sometimes requiring pacemaker implantation in case of a complete heart block.

The lungs

Pulmonary involvement in RA includes pleural lesions, lung nodules, and interstitial lung disease. Pleural involvement is the most common manifestation of lung disease in RA, it has been shown up to 50% on autopsy, but is usually asymptomatic.

In AS, pulmonary complications are infrequent and can be caused by rigidity of the chest wall. Recent studies with high resolution computed tomography (HRCT) detected interstitial lung disease in 50–70% in early AS, with a disease duration of <10 years (26).

The gastrointestinal tract

Both, in RA and AS, peptic ulcers and mucosal lesions due to the use of NSAID's are a common problem, but the preventive use of protonpump inhibitors and use of selective COX-2 inhibitors have decreased this risk (27).

In AS, asymptomatic inflammatory bowel disease was described in a high percentage of patients (60%), detected by endoscopy of the colon and terminal ileum (28). During follow up studies it appeared that up to 25% of these AS patients with peripheral arthritis and chronic gut inflammation eventually develop Crohn's disease (29). On the other hand, Crohn's disease and ulcerative colitis (inflammatory bowel diseases, IBD) can manifest with sacroiliitis and peripheral arthritis, resembling AS.

Rare extra-articular manifestations

In RA, small vessel vasculitis is relatively uncommon (<5%) and is generally restricted to the digits with nailfold lesions. Systemic vasculitis occurs in a minority and is associated with a severe RA and associated with an increased mortality (30).

Felty's syndrome is characterised by neutropenia and splenomegaly and occurs in a minority of the RA patients with a severe disease. In AS, vasculitis and Felty's syndrome do not occur.

Laboratory tests

Laboratory test in RA reveal increased acute phase reactants, such as ESR and CRP, much more often than in AS (Table I), despite high disease activity in AS (31).

For RA serological markers such as the IgM rheumatoid factor and the more specific anti-CCP antibodies are often present: in hospital based groups of patients with early RA, the prevalence of RF is 50–66%, and the prevalence of anti-CCP is 41–48%. Remarkably, it has been shown that 49% of the patients were positive for IgM-RF and/or anti-CCP on at least one occasion before the development of RA symptoms, a median of 4.5 years before the symptom onset (32).

In AS, the IgM rheumatoid factor and anti-CCP are undetectable in most cases. The HLA-B27 antigen can be helpful in establishing the diagnosis of AS in clinically undetermined cases and is most often absent in RA.

Radiology

In RA, radiographs of the hand and feet joints show typical joint space narrowing due to loss of cartilage and bony erosions (Table I). Radiographic changes, showing erosions of the hands and feet can occur within 6 months after the first symptoms (33, 34) (Figs. 1 and 2).

The radiographic features of the inflamed joints in AS might be similar to rheumatoid arthritis, but in AS, bony ankylosis of the wrists, tarsal bones, hips and small joints of the fingers and toes is a more prominent feature than erosions. Sacroiliitis is the most important characteristic of AS and can be detected by a conventional radiograph of the pelvis



Fig. 1. X-ray feet of rheumatoid arthritis: erosions of the MTP joints



Fig. 2. X-ray hands of rheumatoid arthritis: erosions of the PIP, MCP joints and joint space narrowing of the wrists



Fig. 3. X-ray lumbar spine of ankylosing spondylitis with bilateral sacroiliitis (grade IV), syndesmophyte formation and bamboo spine.

which shows blurring of the distal part of the SI-joints, progressing to joint space narrowing and finally ankylosis of the joints (Fig. 3). At an early stage of the disease Magnetic Resonance Imaging (MRI) is more sensitive to reveal signs of active SI-inflammation and Computed Tomography (CT) to detect early chronic bony changes, compared with conventional radiographs (35, 36).

Sacroiliitis is virtually always absent in RA.

The spinal inflammation in AS coincides with the formation of syndesmophytes and squaring of the vertebrae, sometimes evolving into the classical bamboo spine (Fig. 3), which can be seen at the x-rays of the cervical, thoracic and lumbar spine.

Differential diagnosis

The list of differential diagnoses of RA is extensive (table III). Important is to differentiate from psoriatic arthritis, which can manifest as a polyarthritis

or resembling ankylosing spondylitis with spinal complaints.

Psoriatic arthritis occurs in 5–20% of the people with psoriasis and can present as a symmetrical polyarthritis, resembling RA, but with additional involvement of the DIP-joints (instead of the PIP-joints only in RA) and without a positive rheumatoid factor.

Axial disease occurs in about 5% of the psoriasis patients with asymmetrical sacroiliitis in one-third of the patients and spondylitis without sacroiliitis in the rest. Enthesitis is common, especially in the oligoarticular form of the disease. The radiographic features of psoriatic spondylitis show more or less random syndesmophyte formation, whereas in AS, syndesmophytes form in a more ascending fashion (37).

Other autoimmune diseases, such as SLE, polymyalgia reumatica, etc., but also viral infections, can resemble RA (Table III).

AS belongs to a group of diseases which are referred to as Spondylarthritides (SpA, Table IV). The group of SpA includes rheumatoid factor negative patients with inflammatory back pain and/or asymmetrical synovitis, like psoriatic arthritis, arthritis accompanying inflammatory bowel disease (*e.g.* Crohn's disease) and reactive arthritis. SpA is diagnosed according to the criteria of the European Spondylarthropathy Study Group (ESSG) (38), which require inflammatory spinal pain or synovitis plus a positive family history of psoriasis or inflammatory bowel disease or alternate buttock pain or enthesiopathy or sacroiliitis. Most recently, new ASAS classification criteria for axial SpA have been published covering both patients with established AS and patients with early non-radiographic AS (39). In these criteria the presence of sacroiliitis either on x-rays or MRI (active inflammation) play a crucial role.

In 10–20% of patients with IBD, like ulcerative colitis and Crohn's disease, peripheral arthritis of the knees, ankles and feet occurs (40). In 10% of the patients with IBD sacroiliitis or spondylitis occurs and is often asymptomatic (40). The course of the spondylitis is independent of the active bowel inflammation.

Diffuse idiopathic skeletal hyperostosis (DISH or Forestier's disease) can resemble AS because of the stiffness of the spine due to hyperostosis of the anterior longitudinal ligaments and bony attachments of the tendons. However, in contrast with AS, the onset of the disease is at a later age (over 50), there is no association with HLA-B27 and SI joints are seldomly involved.

Course and prognosis

Disease severity of RA used to be higher in males compared to females with more frequent and earlier erosive disease and a higher frequency of rheumatoid nodules.

In AS, overall disease manifestations in men are most commonly located in the spine and pelvis, whereas women have more symptoms in the peripheral joints and pelvis (41).

AS tends to be more severe in men, with a higher incidence of uveitis (27)

Table III. Differential diagnosis rheumatoid arthritis.

Other diseases with (poly-)arthritis
Polymyalgia rheumatica
Remitting seronegative symmetrical synovitis with oedema (RS3PE syndrome)
Psoriatic arthritis
Adult-onset Still's disease
Systemic lupus erythematosus (SLE)
Hemochromatosis
Viral induced arthritis (Parvovirus)
Crystal-induced synovitis
Septic arthritis
Reactive arthritis
<i>etc.</i>

Table IV. Differential diagnosis ankylosing spondylitis.

<i>Other types of spondyloarthritis</i>
Psoriatic arthritis
Inflammatory bowel disease: ulcerative colitis or Crohn's disease
Reactive arthritis
Juvenile spondyloarthritis
<i>Other types of arthritis</i>
Rheumatoid arthritis
<i>Other causes of back pain</i>
Non-inflammatory back pain
Fibromyalgia
Spine diseases: prolapsed intervertebral disc, spinal tumours, bone tumours
Infections: tuberculosis a.o.
Metabolic diseases
Diffuse idiopathic skeletal hyperostosis (DISH or Forestier's disease)
<i>Other causes of sacroiliitis</i>

and more radiographic progression (42), but the results are contradictory. In females, radiological changes of the cervical spine are more commonly reported than in men, as well as spondylitis (25).

RA, like in most cases of AS, can have an insidious onset of the disease in approximately 70% of the patients. Abrupt onset of RA may occur in 10–15% of patients. Persistent erosive disease in early arthritis patients can be predicted by anti-CCP positivity, bilateral compression pain of the MTP joints and bony erosions within 2 years after the onset of complaints (2).

Early detection and treatment has improved the course and outcome of RA dramatically during the last decades, by 'Early Arthritis' clinics for instance. Moreover, tools for pre clinical detection of RA, based on family history and serological tests with rheumatoid factor and anti-CCP are very useful to predict the onset of RA in patients suffering from arthralgia (32). Early treatment with DMARDs, corticosteroids, and TNF blocking agents have reduced the

loss of function and irreversible joint damage. Several combination therapies and regular monitoring and adapting treatment with the Disease activity Scores (DAS) for RA have shown to decrease the radiographic progression which results in lower number of joint number of joint prostheses (43).

In order to reduce the delay in the diagnosis of AS as well, an algorithm was developed recently by Rudwaleit *et al.* including inflammatory back pain, HLA-B27 and a family history of spondyloarthritis in order to detect early cases of AS (44).

In many cases the disease outcome of AS is favorably, but approximately one third of the patients develop disabling deformities (7). Predictors of a severe outcome are hip arthritis, an increased erythrocyte sedimentation rate, (ESR >30 mm/h), peripheral arthritis and a juvenile onset (≤ 16 years). The rate of radiological progression appears to be constant during the several decades of the disease duration (45).

In contrast with RA, DMARDs are proven to be not effective in AS, except for

sulfasalazine which is beneficial in case of peripheral arthritis (46, 47). During many years Non Steroidal Anti-Inflammatory Drugs (NSAIDs) and physical therapy were the only treatment options to improve the long-term outcome of AS. However, the therapeutic possibilities in AS have changed since the introduction of biologicals, especially drugs that block the effect of the pro-inflammatory cytokine Tumor Necrosis Factor (TNF) α . Large placebo-controlled trials (48-50) confirmed the efficacy of these biologicals in these patients on disease activity, as well as in regression of MRI-changes (51). Data concerning the long term outcome in AS with TNF blocking agents are limited but they seem to be very effective in remaining functional capacity and reducing disease activity in AS.

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Enthesal involvement

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Received and accepted on July 29, 2009.

Clin Exp Rheumatol 2009; 27 (Suppl. 55): S50-S55.

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EXPERIMENTAL RHEUMATOLOGY 2009.

Key words: Enthesitis, spondyloarthritis, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, power Doppler ultrasonography, magnetic resonance imaging, conventional radiography.

ABSTRACT

Enthesitis is a distinctive pathological feature of spondyloarthritis and may involve synovial joints, fibrocartilaginous joints, syndesmoses and extra-articular entheses. Extrarticular pain may often be present in rheumatoid arthritis patients. This review focuses on peripheral enthesitis which is a clinical hallmark of spondylarthritis, by comparing the same findings in rheumatoid arthritis.

Introduction

Entheses represents the sites of insertion of tendon, ligament, fascia or joint capsule to bone. Recent knowledge regarding the function, anatomy and physiology of the enthesis has led to improve our understanding of enthesal pathology in the course of many inflammatory and non-inflammatory rheumatic diseases. The involvement of enthesis in any pathologic process, whether metabolic, inflammatory, traumatic or degenerative, is referred to as “enthesopathy”, while “enthesitis” is restricted to the inflammatory enthesopathy, and it appears to be a cardinal feature of spondylarthritis (SpA) (1, 2). Although Niepel *et al.* first used the term for describing inflammatory symptoms at insertional sites as an important feature of ankylosing spondylitis (AS) (3), enthesitis is a common characteristic feature of all the SpA complex which also include psoriatic arthritis (PsA), reactive arthritis (ReA), arthritis associated with inflammatory bowel disease (IBD) and the undifferentiated forms (4, 5). Ball firstly suggested in his famous “Heberden oration” that AS and rheumatoid arthritis (RA) differ primarily in the diverse target organs (6). He suggested that inflammation at the enthesis is the distinctive pathological feature of AS (5-8). In contrast, the characteristic feature of RA is a persistent inflammatory synovitis involving mainly the peripheral joints symmetrically (9).

Since this first observation several authors have tried to evaluate whether differences exist between AS and RA in the enthesal involvement (1, 10).

Although axial and peripheral skeletons are a target for both SpA and RA, and any enthesis all over the body can be involved, some insertions seem more important than others for distinguishing between these two inflammatory diseases (10-13).

The purpose of this review is to explore articles looking for enthesitis in RA and AS, to describe the differences in clinical aspects of enthesitis in AS as compared to RA and to discuss the imaging appearance of enthesal involvement in both diseases.

Are entheses involved in RA?

Based on clinical symptoms, extrarticular structures are frequently involved in RA. The trochanter region, heels and hands are reported as the most painful sites (10, 14-16). This involvement seems primarily related to the synovial membrane lining the tendon sheaths and the bursae (10, 17, 18). In the hand, tenosynovitis of both the extensor and the flexor tendon is frequently observed. A trigger finger is often associated with digital sheath tenosynovitis as a consequence of the location of a rheumatoid nodule inside the tendon. Tendon involvement seems to be an early finding of RA (18) and may be predictive for future tendon rupture (19). Actually, persistent hand tenosynovitis may lead to tendon rupture especially of the extensor tendon of the ring and little fingers and of the flexor pollicis longus. In the forefoot, the synovial sheaths of the flexor tendons are usually involved together with the metatarso-phalangeal joints. With regard to the bursae, the most frequently involved include the subacromial, olecranic, iliopectoral, trochanteric, ischial, gastrocnemius, semimembranosus and retrocalcaneal (18). The involvement of entheses has been the object of several studies performed

Competing interests: none declared.