Chapter from the book *Clinical and Molecular Advances in Ankylosing Spondylitis*

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1. Introduction

Ankylosing spondylitis is an inflammatory rheumatic disease, its cause is yet unknown, a cross-reactivity of antibodies against germs and HLA-B27 is discussed, but not yet proven. Ankylosing spondylitis belongs to the group of seronegative spondyloarthritides (Moll J, Haslock I, Mac Rae IF, Wright V) (Wright V), there is a strong linkage to HLA-B27. Its prevalence lies between 0.1% and 1% with a male predominance of 2:3:1, the onset of disease lies between 20 and 40 years, very seldom above the age of 45 (Wolf J, Fasching P). So women are less frequently concerned, and the illness tends to take a milder course (Sieper J, Braun J, Rudwaleit M, Boonen A, Zink A) (Gladman DD). On the other hand this puts women to a disadvantage, as the disease is less easily detected, leading to an even longer interval between disease onset and treatment.

General symptoms include morning stiffness of more than 60 minutes, fatigue, sometimes even slightly elevated temperature, but the main initial symptom is low back pain at night and in the morning. All patients with low back pain should be questioned about a positive family history concerning rheumatic diseases, as the risk of developing this illness is higher in patients where family members already have been diagnosed with ankylosing spondylitis. This of course suggests a certain genetic disposition, especially if HLA-B27 is involved (Van der Linden SM, Valkenburg HA, De Jongh BM, Cats A).

As a systemic inflammatory disease it is not restricted to a single organ or part of the body. The following subchapters will deal with the different manifestations of this disease.

2. Spinal manifestations

The first symptoms of this disease are usually a low back pain with its peak at night and in the morning and morning stiffness, which can last for hours. Both symptoms get better with exercise, back pain can worsen with inactivity. Some patients show only a partial involvement of the spine, in others the whole spine is involved. The physician always should examine the patient’s back by patting it gently with one fist, starting at the cervical spine all the way down to the sacrum, asking the patient, if and which part of the spine is painful during this examination.

The disease is caused by chronic inflammation of the spinal joints and entheses, proliferative synovitis and central cartilage fusion, which can lead to total destruction and ankylosis of
these joints. Fibroblast proliferation on the other hand leads to increased ossification creating syndesmophytes (Figure 1) between the vertebral bodies and later on bamboo spine (Figure 2). These cause an irreversible loss of spinal flexibility and movement, resulting in the typical habitus still to be seen in older patients with a long disease duration due to significantly enhanced kyphosis of the thoracic part of the spine and loss of lordosis of the lumbal spine, finally making it impossible for the patient to bend any part of his spine.

Inflammation can also be found in the intervertebral disks resulting in discitis and spondylitis, which can be seen as narrowing of the intervertebral space and destruction of the adjacent cover plates. Seldom synovitis and osteitis can be found in the atlantoaxial area leading to erosions and destruction of the lateral atlantoaxial joint. At the worst the joint is destabilized, this may cause cord compression and neurological loss of function.

The costovertebral and costotransverse joints are quite commonly affected, being causal to reduced chest expansion and decreased vital capacity of the lungs.

In some patients ankylosing spondylitis is restricted exclusively to an affection of the sacro-iliac articulation (sacroiliitis), best shown by MRI, as it causes bone marrow edema and cartilage changes. X-ray takes a long time to reveal this arthritis, because there only bone destruction and ankylosis are visible, these are not seen in the early stages of the disease. In the end sacroiliitis can lead to total destruction and ankylosis of the sacroiliac joint, then of course it is clearly visible in x-ray (Figure 3). Active sacroiliitis can lead to local pressure pain and pain associated with movements of the pelvis.

Finally kyphosis of the thoracic spine, obliteration of the lumbal lordosis and forward stoop of the neck occur, these signs are irreversible. Due to osteoporosis even minor trauma may result in spinal fractures, causing a rapid and significant increase in pain. Fracture fragments can be dislocated and lead to cord compression.

3. Peripheral joints

Almost half of the patients experience arthritis in the hips or the shoulders. Up to 30% of the patients suffer from small joint involvement with swelling, pain and stiffness in the inflamed joints. Often these appear as asymmetrical oligoarthritis. Usually they are non-erosive, but deformity and consequently destruction of the hips have been seen. An early involvement of peripheral joints can be an indicator of a more aggressive progress. Peripheral joint involvement can occur at any stage of the disease (Sieper J, Braun J, Rudwaleit M, Boonen A, Zink A) (Gladman DD).

4. Extra-articular manifestations

Quite common there is an involvement of the enthesis, meaning the insertion of tendons, ligaments and capsules into the bone. These inflammatory changes are referred to as enthesitis (Francois RJ, Braun J, Khan MA). Any enthesis may be concerned, but most frequently an enthesitis of the Achilles tendon is found. Enthesitis causes pain, swelling and thickening as well as loss of function, it can occur all of a sudden, but is found quite often as a chronic inflammation, which can finally lead to rupture of the tendon. Arthritis of the adjacent joint has also been described, enthesitis is presumed to be the starting point of joint inflammation (McGonagle D, Gibbon W, Emery P)
Fig. 1. Syndesmophytes.
Fig 2. Bamboo stick.
Up to 40% of all patients suffer from acute anterior uveitis at least once in their lifetime (Rosenbaum JT). Uveitis occurs usually unilateral, symptoms include pain, redness, reduced sight, photophobia, grittiness, myosis and increased lacrimation. It is self-limiting, but tends to reoccur. Untreated it may lead to complications like synechia and cataract. Patients have to be advised to see a doctor immediately after onset of the above mentioned symptoms.

Another extra-articular manifestation is aortitis and/or aortic regurgitation. Approximately 9% of ankylosing spondylitis patients are concerned. Aortitis can be seen in echocardiography showing thickening of the aortic wall and dilatation of the aortic root, thickening of the aortic valves causing aortic insufficiency (2-10% of the patients). 1-9% acquire a complete heart block, mainly located in the atrioventricular node (Bergfeldt L).

The lungs are usually only concerned indirectly because of involvement of the costovertebral and costotransverse joints and therefore reduction of chest expansion leading to reduced vital capacity. This can be detected by pulmonary function testing. But pulmonary participation like upper lobe fibrosis and pleural thickening has been described, these can be detected by high-resolution computed tomography (Maghraoui AE, Chaouir S, Abid A et al) (Souza AS, Muller NL, Marchiori E, Soares-Souza LV). These findings are usually clinically asymptomatic, yet fibrosis tends to progress over time.

4-9% of the patients develop a secondary renal amyloidosis as part of the autoimmune disease, yet primarily, renal involvement is rather uncommon in ankylosing spondylitis. Renal amyloidosis may occur in patients with long disease duration (Nabokov AV, Shabunin MA, Smirnov AV).

Due to chronic pain, patients with ankylosing spondylitis often depend upon painkillers. Especially non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed, as these agents
reduce pain, but also inflammation itself. Long-term intake of this medication is generally recommended, as trials have shown a significantly better effect on pain in comparison to placebo (Dougados M, Dijkmans B, Kan M, Maksymowych W, Van der Linden S, Brandt J) (Van der Heijde D, Baraf HS, Ramos-Remus C et al). Some studies even reported a decrease of spinal ossification, if the drug was taken on a regular basis (Boersma JW) (Wanders A, Van der Heijde D, Landewe R et al). On the other hand, NSAID induced nephropathy can occur in older patients with a longer disease duration and after several weeks or months of NSAID use, independent of the primal medical cause for painkillers. NSAIDs have to be discontinued in these cases. However, renal parameters should be checked on a regular basis in all patients with ankylosing spondylitis.

In up to half of the patients osteoporosis can be found, yet DEXA can be falsified by syndesmophytes, creating the impression of a higher bone density. Bone fracture caused by even minor traumatic events can lead to a sudden increase of pain. The same applies to fractures of the syndesmophytes themselves. Most frequently fractures of the cervical spine are observed, followed by the thoracolumbar region (Feldtkeller E, Vosse D, Geusens P, Van der Linden S). Osteoporosis may be induced by an imbalance between osteoblasts and osteoclasts in favour of the osteoclasts (Obermayer-Pietsch BM, Lange U, Tauber G et al). Decreased mobility may also play its part in the development of osteoporosis.

5. Disease impact

Fatigue and sleeping disorders are quite common in patients with ankylosing spondylitis (Jones SD, Koh WH, Steiner A, Garrett SL, Calin A) (Hultgren S, Broma JE, Gudbjornsson B, Hetta J, Lindqvist U), they can even lead to depression (Barlow JH, Macey SJ, Struthers GR) as well as reduced fitness and working capacity. Fatigue is a typical symptom of ankylosing spondylitis, therefore it has been included in the BASDAI, a patient’s questionnaire (Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A). It seems to correlate with disease activity (Günaydin R, Göksel Karatepe A, Cesmeli N, Kaya T) and aggravates the difficulties patients already experience in daily life activities due to pain and reduced mobility. Sleep disturbance is caused by low back pain that typically begins at night and keeps the patient from having a restful sleep, but also by depression and anxiety. The combination of chronic disease, chronic pain and ensuing disability can lead to depression, for the patient is no longer able to perform activities of daily life the way he or she wishes to and may not be able to work full-time or even fears to lose his or her job because of reduced mobility and flexibility. Ankylosing spondylitis has a highly individual disease course and duration, some patients show only minor symptoms and restrictions, while others suffer very badly. Work disability is higher in patients with longer disease duration, inflammation of peripheral joints, lower level of education, high pain levels and physically straining jobs. Patients with long disease duration and difficult to treat back pain are more prone to develop depression than patients with no or only light pain and symptoms (Baysal O, Durmus B, Ersoy Y, Altay Z, Senel K, Nas K, Ugur M, Kaya A, Gür A, Erdal A, Ardicoglu O, Tekeoglu I Cevik R, Yildirim K, Kamnli A, Sarac AJ, Karatay S Ozgocmen S). The degree of disease activity also seems to correlate with anxiety and health status. Patients with higher disease activity scores were more anxious and more depressed (Martindale J, Smith J, Sutton CJ, Grennan D, Goodacre L, Goodacre JA).
Neurological symptoms are caused by complications of long-ongoing disease. Due to osteoporosis spinal fractures may occur, leading to suddenly increasing back pain in the afflicted region. If a fracture fragment is dislocated, it may injure the spinal cord and subsequently cause neurological symptoms. The cauda equina syndrome is evoked by dural ectasia, usually a late manifestation of the illness (Ahn NU, Ahn UM, Nallamshetty L, Springer BD, Buchowski JM), leading to sensory and/or motor loss of function and finally sphincter dysfunction. Patients may also develop pain in the rectum or the lower limbs. Atlantoaxial subluxation on the other hand may cause neurological symptoms in one or both arms. 2% of all patients with ankylosing spondylitis are concerned, but not all of them show signs of cord compression (Chou LW, Lo SF, Kao MJ, Jim YF, Cho DY). Subluxation may be caused by transverse or posterior longitudinal ligament damage or local atlantodental synovitis as well as somatic stress caused by increased kyphosis of the cervical spine.

6. Ankylosing spondylitis and other seronegative spondyloarthritis

Ankylosing spondylitis belongs to the group of seronegative spondyloarthritis together with psoriatic arthritis, reactive arthritis and unspecified spondyloarthritis. They all lack rheumatoid factor, thus being seronegative. Ankylosing spondylitis has also been seen in combination with psoriatic arthritis or enteropathic arthropathies like Crohn’s Disease and ulcerative colitis.

Peripheral asymmetrical arthritis is seen in approximately 50% of patients with psoriatic arthritis. As this disease can also include axial manifestations, a thorough skin examination has to be done in any patient with low back pain. 20 to 40% of patients with psoriatic arthritis suffer from sacroiliitis (Gladman DD, Shuckett R, Russell ML et al) (Torre Alonso JC, Rodriguez Perez A, Arribas Castrillo JM et al). There is also a tendency of cervical spine involvement and asymmetrical affliction (Jenkinson T, Armas J, Evison G et al). Psoriatic arthritis can cause monoarthritis, dactylitis, asymmetrical oligoarthritis and enthesitis, up to 25% of patients with psoriatic arthritis are HLA-B27 positive, but in patients with spinal inflammation up to 70% are HLA-B27 positive. On the other hand, there are patients who show no or only minimal skin affection at the onset of arthritis, making it even more difficult to find the right diagnosis. The transition between these two diseases is gradual and can differ greatly between two individuals. Some patients show definite signs and symptoms of ankylosing spondylitis with only marginal involvement of the skin and peripheral joints, others mainly present skin and joint affections with only little back pain. In these cases, it is quite easy to diagnose ankylosing spondylitis in combination with psoriasis or psoriatic arthritis with axial manifestations. But other individuals are not as easily diagnosed, especially if all symptoms are equally strong or weak or if there is no skin involvement at all. So sometimes it can be difficult even for the rheumatologist to differentiate between these two diseases. Yet this is of importance concerning the choice of treatment: while psoriatic arthritis can be treated with Disease Modifying Anti-Rheumatic Drugs (DMARDs) like Methotrexate or Leflunomide, these agents have no effect on peripheral arthritis caused by ankylosing spondylitis.

Spondyloarthritis can be found in both Crohn’s Disease and ulcerative colitis. The incidence lies at 1-12%. Up to 50% of the patients also develop peripheral arthritis. Both are autoimmune diseases, yet the pathogenesis is still largely unclear. Peripheral arthritis can
appear before the onset of bowel symptoms, causing acute, but self-limiting attacks of monoarthritis or asymmetrical oligoarthritis as well as chronic arthritis. Hips and shoulders are less frequently affected as in ankylosing arthritis. A flare of the bowel disease can be accompanied by another flare of arthritis. Enthesitis of the Achilles tendon has been reported. Sacroiliitis can occur asymptomatic or with the typical signs of low back pain, stiffness and reduction of spinal mobility. Spondylitis is independent of gut flares. Up to 50% of patients with ankylosing spondylitis on the other hand are diagnosed with gut inflammation when examined by colonoscopy (De Kaiser F, Baeten D, Van De Bosch F et al).

Reactive arthritis is another disease belonging to the group of seronegative spondyloarthritides and usually leads to asymmetrical peripheral arthritis lasting for several months up to one or two years. Acute inflammation, swelling and pain of the joints, dactylitis and enthesitis are the main symptoms. Any joint can be affected, but most commonly knees, ankles and metatarsophalangeal joints. Later on, osteoarthritis may develop in formerly affected joints. Patients also suffer from fatigue, fever and malaise. Low back pain is rather common in these patients, caused by acute sacroiliitis, enthesitis and muscle tension. Spondylitis and sacroiliitis tend to be asymmetrical, but normally they do not lead to spinal fusion and ankylosis. There is a correlation between reactive arthritis, HLA-B27 and a previous infection (Khan MA) (Silman AJ, Hochberg MD), yet no germ can be found in any of the affected joints. Skin and mucous membrane lesions, sterile urogenital inflammation, sterile conjunctivitis, but also acute anterior uveitis and keratitis may occur (Saari KM). As ocular manifestations tend to reoccur, patients have to be advised to see an ophthalmologist immediately upon onset of ocular symptoms. X-ray will not be very helpful in acute sacroiliitis, but it can help to detect signs of previous sacroiliac inflammation. Back pain may persist even after disappearance of arthritis. In some patients ankylosing spondylitis subsequently evolves, but it is unclear whether reactive arthritis is the predecessor or if this is just a coincidence. Reactive arthritis tends to show a more aggressive and longer disease course when HLA-B27 positive, but at least 50% are HLA-B27 negative, so it should not be tested on a regular basis, as the result could be misleading.

7. Clinical measurements for ankylosing spondylitis

In order to evaluate pain, morning stiffness and functional ability two different questionnaires have been developed: the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and the BASFI (Bath Ankylosing Spondylitis Functional Index). Both are questionnaires that have to be completed by the patient.

The BASDAI (Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A) consists of 6 questions, they deal with fatigue, pain and morning stiffness during the last week. The questions have to be answered on a scale from 0 to 10. The patient has to tick the box with the appropriate number. 0 means no fatigue / pain / morning stiffness at all, 10 would be the worst possible case.

The BASFI (Calin A, Garrett S, Whitelock H et al) is meant to evaluate functional impairment. 10 questions are asked about the patient’s ability to dress, to bend forward, to reach up, to stand up, use the stairs, do physical labour, sports and a full day’s activities. Once again a scale from 0 to 10 is used. 0 means no problems at all, 10 means that the patient is not able to perform these activities.
As these two tests have to be filled out by the patient, they are very useful to evaluate how the patient is feeling overall and faring at work and at home. They can be redone at every visit to check, if there is an improvement or worsening of symptoms and mobility.

There are several easy to do measurements for the spine that can be evaluated at any visit and by every physician (Van der Heijde D, Bellamy N, Calin A, Dougados M, Khan MA, Van der Linden S). These examinations are important to check and control spinal function and flexibility, as ankylosing spondylitis is characterized by increasing ankylosis and loss of spinal flexibility and mobility. The rheumatologist can use these measurements to check on a possible progress of the illness or the success of an ongoing therapy. They can be easily done and redone at any given time. All that is necessary is a measuring tape and a pen.

The first test is called Schober (Schober P) (Viitanen JV, Heikkila S, Kokko ML, Kautiainen H). This gives evidence about the lumbar spine flexion. The patient has to stand straight, a sign is made over the spine at the height of the posterior superior iliac spines, a second sign 10 cm above the first (Figure 4). Then the patient has to bend forward with locked knees as far as possible, and the distance between the two marks is measured. A healthy and flexible lumbal spine shows an increase of this distance of at least 5 cm. An increase of 4 cm or less correlates with a restriction of movement of the lumbal spine.

A variation of the Schober test is the modified Schober test. When using the modified Schober test another mark is set 5 cm below the posterior superior iliac spines, then the distance between this point and the one 15 cm above is measured. There should be a difference of 20 cm at least (Mcrae IF, Wright V).

Lateral lumbar flexion can also be tested. The patient leans against the wall placing his or her hands to the side of his legs. The end of the middle finger is marked, then the patient is asked to bend laterally with straight knees towards the marked side as far as possible. The difference between start and endpoint of the middle finger is measured. A distance of more than 10 cm means normal lateral flexibility.

The next test is called Ott. Here the flexibility of the thoracic spine is measured. Once again, the patient has to stand upright. The seventh cervical spine is marked, then the second mark is applied 30 cm below the first one. Then the patient has to bend forward again as far as possible, and once again the distance between the two marks is measured. The distance should increase at least to 33 cm in order to show a normal movement of the thoracic spine.

Then the patient should stand against the wall, heels and shoulders touching the wall. The patient is asked to move his head backwards, until his occiput touches the wall (Heuft-Dorenbosch L, Vosse D, Landewe R, Spoorenberg A, Dougados M). Patients with decreased cervical movement are not able to do so, in this case the distance between the back of the head and the wall is measured. Any distance is pathological. Next the patient is asked to move his chin towards his breast, thus measuring the ventral flexibility of the cervical spine. The chin should touch the breast, any measurable distance is an indication for reduced agility of the cervical spine.

Next one can also measure the distance between fingertips and floor. In this case the patient has to bend his back forward with unbent knees as far as possible, until the fingertips touch the floor. This test is a general test of spinal flexion, but untrained people or patients with non-inflammatory diseases like spondylosis deformans or discopathy are quite often not able to reach the floor as well.
Another easy but very important test is the measurement of chest expansion. Chest circumference is measured at the height of the forth intercostal space in expiration, then in maximum inspiration. Normally there is a difference of 5 cm or more. Decreased chest expansion in patients with ankylosing spondylitis can lead to breath shortness, reduced exercise tolerance and reduced vital capacity of the lungs. Patients with a reduced chest expansion should be checked regularly by pulmonary function testing.

Fig. 4. Schober test.

8. Conclusion

Ankylosing spondylitis is a chronic inflammatory rheumatic disease. This disease – as all inflammatory rheumatic diseases – shows a great variability and individuality concerning symptoms, progress and outcome and is not limited to axial manifestation and affliction of the entheses, but may also involve peripheral joints, inner organs like the heart, lungs, kidneys and eyes and is associated with fatigue and depression.

So it can be quite difficult even for the rheumatologist to find the right diagnosis from the start. So every doctor should keep in mind to send each patient with low back pain during the night and in the morning, morning stiffness and reduced flexibility of the spine to a rheumatologist.

9. References

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The first section of the book entitled Clinical and Molecular Advances in Ankylosing Spondylitis is a review of the clinical manifestations of Ankylosing Spondylitis (AS) and Spondyloarthritis (SpA). The book includes chapters on Bone Mineral Density measurements, two chapters on the temporomandibular joints, axial fractures, clinical manifestations, diagnosis, and treatment. Molecular genetics and immune response are analyzed in the second section of the book; information on HLA-B*27, other MHC genes and the immune response of AS patients to bacteria is reviewed and updated. Two chapters are dedicated to recent information on non-MHC genes in AS susceptibility, and to new data on disease pathways generated from gene expression studies on peripheral blood.

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