Review Article

A review on ankylosing spondylitis

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Abstract

Ankylosing spondylitis (AS) is a long-term inflammation of the joints of the spine which is complex, potentially debilitating disease that is insidious in onset, progressing to radiological sacroiliitis over a period of years. The pathogenesis of AS is poorly understood. However, immunomediated mechanisms involving human leukocyte antigen-B27, inflammatory cellular infiltrates, cytokines like tumor necrosis factor α and interleukin-10, and genetic and environmental factors are thought to have key roles. The presence of inflammatory back pain plus at least two other typical features of spondyloarthropathy such as enthesitis and uveitis is highly predictive of early AS. Nonsteroidal anti-inflammatory drugs (NSAIDs) effectively relieve inflammatory symptoms and are presently first line drug treatment. However, NSAIDs have an influence only on the symptomatic effect and has no effect on the disease. For symptoms unresponsive to NSAIDs, the second-line treatment includes corticosteroids and various disease modifying antirheumatic drugs are used.

Keywords: Ankylosis, human leukocyte antigen, nonsteroidal anti-inflammatory drugs, spondylitis arthopathies, tumor necrosis factor-alpha

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INTRODUCTION

Ankylosing spondylitis (AS) is from Greek ankylos - fused; spondylos, vertebrae;-itis, inflammation. Earlier it was known as Bechterew's disease/syndrome and Marie-Strümpell disease. AS is a form of spondyloarthritis, a chronic inflammatory arthritis[1] where immune mechanisms play a role.[2] It mainly affects joints in the spine and the sacroiliac joint (SIJ) in the pelvis and can result in fusion of the spine eventually. Complete fusion results in a complete rigidity of the spine, a condition known as bamboo spine. AS is a complex and debilitating disease with a worldwide prevalence ranging up to 0.9%. Its etiology and pathogenesis are not yet fully understood and its diagnosis is difficult. As a result, the management and treatment is often unsatisfactory. Improvements are made by comprehensive knowledge of history, pathogenesis, diagnosis, treatment, natural course, and socioeconomic impact of the disease. There is no cure although treatments and medications can reduce symptoms and pain.[3-5]

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SIGNS AND SYMPTOMS

Symptomatic changes are gradual and usually occur around 23 years of age.[6] Initial symptoms are typically chronic pain and stiffness in the middle part of the spine or the entire spine, often with pain referred to one or the other buttock or the back of the thigh from the SIJ. Since the initial signs and symptoms are not specific for AS, there is a lag-time between onset of disease and diagnosis, which averages between 8.5 years and 11.4 years. About 40% of patients experience inflammation in the anterior

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chamber of the eye, causing redness, eye pain, floaters, and photophobia. Visual acuity is usually maintained, and the fundus is normal. Other common symptoms include chest pain and generalized fatigue. Less commonly, aortitis, aortic valve insufficiency, apical lung fibrosis, and ectasia of the sacral nerve root sheaths may occur. In patients aged less than 18 years, it causes pain and swelling of the Knee. In prepubescent cases, pain and swelling may be present in the ankles and feet.

EPIDEMIOLOGY

Age of onset

AS commonly starts in the second or third decade of life.[7,8] A survey of 3000 German patients with AS showed the following distribution pattern of age at the time of first spondylitic symptoms: 4% were younger than 15 years; 90% were 15–40 years; the remaining 6% were more than 40 years.[9] Analysis of a German rheumatological database (n = 8776) determined a mean age at onset of AS of 28.3 years.[10,11]

Sex

Men are afflicted approximately two to three times more frequently than women. Estimated percentages of male patients among the AS patient population range from 65% to 80% and vary by geographic location (68.9% in a German rheumatological database, n = 877,671; and 78.3% in a French study, n = 473).[12] The disease pattern varies by sex. The spine and pelvis is most commonly affected in men, with some involvement of the chest wall, hips, shoulders, and feet. In contrast, women have less severe involvement of the spine, with more symptoms in the knees, wrists, ankles, hips, and pelvis.[3,13,14] Disease also tends to be more severe in men.

Prevalence

For the spondylitis arthopathies (SpAs) as a group, the overall prevalence in the population has been reported to be as high as 1.9%. There is a wide geographic variation in reported estimates of the prevalence of AS. However, in general, there is a close correlation between the prevalence of human leukocyte antigen (HLA)-B27 and the prevalence of SpAs in a given population. Among the total 3.47 million population of Berlin, Germany, the prevalence of AS estimated from an HLA-B27 frequency of 9.3% was reported to be 0.86%. The prevalence of Ankylosing Spondylitis in Finland was 0.15% and 1.1%–1.4% (men 1.9%–2.2%, women 0.3%–0.6%) among adults in Norway.[15,16] The overall prevalence of SpA among adult Eskimo populations in two study regions in Alaska was estimated at 2.5%. Prevalence also appears to vary among ethnic groups. The estimated nationwide prevalence of SpA among the total Japanese population (9.5/100,000) is <1/200 of western countries.[17,18]

PATHOPHYSIOLOGY

AS affects the entire body. Approximately 90% of the patients express the HLA-B27 genotype, which concludes a strong genetic association. 1%–2% of individuals with the HLA-B27 genotype contract the disease.[19] Tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1 are also implicated in AS. Autoantibodies specific for AS has not been identified. Anti-neutrophil cytoplasmic antibodies (ANCAs) are associated with AS, but do not correlate with the severity of the disease. In a study of 40 patients with AS, ANCA was an infrequent finding, being present in six patients.[20] The association of AS with HLA-B27 suggests the condition involves CD8 T cells, which interact with HLA-B. This interaction is not proven to involve a self-antigen, and at least in the related Reiter's syndrome (reactive arthritis), which follows infections; the antigens involved are likely to be derived from intracellular microorganisms. However there is a possibility that CD4 T-cells are involved in an aberrant way, since HLA-B27 appears to have a number of unusual properties, including possibly an ability to interact with T-cell receptors in association with CD4 (usually cytotoxic T lymphocytes with CD8 react with HLAB antigen as it is a major histocompatibility complex Class 1 antigen).

DIAGNOSIS

The diagnosis of AS before the occurrence of irreversible damage is difficult. Several years may pass between onset of symptoms and definite diagnosis. This delay is most likely due to low awareness among nonrheumatologists of AS or SpAs and the fact that radiological proof of sacroiliitis is a late feature of the disease. This is unfortunate as earlier diagnoses might potentially reduce the crippling effects that can occur.

RISK FACTORS

The risk factors that predispose a person to AS include are HLA-B27 seropositivity, family history of AS, male sex, and frequent Gastro intestinal infections. A comparison of relatives of patients with AS and the general population determined that the risk for AS was 16 times greater among HLA-B27 positive relatives (21% had AS) than among HLA-B27-positive individuals from the general population (1.3% had AS).[21-24] The HLA-B27-negative relatives did not have any manifestations of AS. AS occurs mostly in men than women. The deficiency in TNF-α

secretion by T cells, coupled with the increased levels of IL10 also may result in long-term persistence of bacteria, leading to inflammation and subsequent pathogenesis in AS.

CLINICAL MANIFESTATIONS

The first symptoms of AS usually appear in late adolescence or early adulthood. The initial symptom is typically a dull pain that is insidious in onset. The pain is generally felt deep in the buttock and/or in the lower lumbar regions and is accompanied by morning stiffness in the same area that lasts for a few hours, improves with activity, and returns with inactivity. The pain becomes persistent and bilateral within a few months and is usually worse at night. About 5% of patients presenting with chronic inflammatory back pain have AS or another SpA subset.[25] The prognostic importance of inflammatory back pain lies in the likelihood of future progression to definite AS. For some patients, bone tenderness may be the primary complaint or may accompany back pain or stiffness. Arthritis in the hips and shoulders occurs in some patients, often early in the course of the disease. Asymmetric arthritis of other joints, predominantly of the lower limbs, can be present at any stage of the disease. Neck pain and stiffness is characteristic of advanced disease. There are several extra-articular manifestations of AS, the most common condition being acute anterior uveitis. Patients may present with unilateral pain, photophobia, and increased lachrymation. Up to 60% of patients with AS have asymptomatic Inflammatory bowel disease (IBD).[26,27] In some cases, frank IBD will develop. Aortic insufficiency, with possible congestive heart failure, is seen infrequently in patients with AS.

Physical findings

A principal physical finding is loss of spinal mobility, with restrictions of flexion, extension of the lumbar spine, and expansion of the chest. The limitation of motion is disproportionate to the degree of ankylosis because of secondary muscle spasms. Pain in the SIJs may be elicited with direct pressure or movement, but its presence is not a reliable indicator of sacroiliitis. There may be detectable inflammation of peripheral joints. Clinical signs of the disease can range from mild stiffness to a totally fused spine, with any combination of severe bilateral hip involvement, peripheral arthritis, or extra-articular manifestations. A patient's posture undergoes characteristic changes if a severe case goes untreated. The lumbar lordosis is destroyed, the buttocks atrophy, the thoracic kyphosis is exaggerated, and the neck may stoop forward.

Laboratory findings

Although no laboratory test is diagnostic of AS, the HLA-B27 gene is present in about 90%–95% of white patients with AS in central Europe and North America. Only 50%–70% of patients with active disease will have an increased level of C-reactive protein (CRP) and a raised erythrocyte sedimentation rate (ESR).[28-30] However, measurement of the levels of these acute phase reactants appears to have limited value in determining disease activity.[31] Studies have shown a lack of correlation between clinical signs of disease activity (pain, stiffness, and sleep disturbance) and CRP and ESR.[32] Mild normochromic normocytic anemia may be detected. A raised alkaline phosphatase level may be present in severe disease. Above normal serum IgA levels are common. Synovial fluid from affected limbs does not differ in appearance from that of any inflammatory joint disease. Airflow measurements and ventilatory function remain normal in patients with restricted chest wall motion, but vital capacity is decreased and functional residual capacity is increased.

Radiographic findings

Radiological changes reflect the disease process; thus, radiographic sacroiliitis usually becomes apparent at some point during the course of AS. However, many years of disease may pass before unequivocal sacroiliac changes are evident on radiographs. The earliest visible changes in the SIJs are blurring of the cortical margins of the subchondral bone, erosions, and sclerosis. As erosion progresses, the joint space appears wider, and then fibrous and bony ankylosis obliterates the joint. Joint changes usually become symmetric during the course of the disease. The New York grading system for SIJ status is as follows: grade I = suspicious; Grade II = evidence of erosion and sclerosis; Grade III = erosions, sclerosis, and early ankylosis; and Grade IV = total ankylosis. computed tomography (CT) and magnetic resonance imaging (MRI) can detect AS lesions earlier and with greater consistency than plain radiography, but these methods are not routinely employed.[33-35] MRI, which is better than radiography for detection of early sacroiliitis, can be performed if radiographs are negative in patients with clinical signs of AS.[36] A prospective evaluation of the relative sensitivities of MRI, quantitative sacroiliac scintigraphy, and plain radiography in detecting active sacroiliitis in 44 patients with clinical symptoms of inflammatory low back pain plus additional features of SpA found MRI to be the most sensitive imaging technique (95% sensitivity, compared with 19% for plain radiography, and 48% for quantitative sacroiliac scintigraphy). These findings indicate that MRI enables detection of approximately 75% more cases of early sacroiliitis (AS) that would otherwise have been missed by plain radiography. CT or MRI may also be useful tools for monitoring progression of SIJ sclerosis. Overall, radiographic (CT and plain radiography) findings

do not correlate well with disease activity. In one study, pain and stiffness correlated positively with an increase in SIJ sclerosis detected by CT and negatively with increasing ankylosis.

Diagnostic criteria

Inflammatory back pain, according to Calin *et al.*, is present if four of the following five features are present: (a) age at onset <40 years; (b) back pain >3 months; (c) insidious onset; (d) morning stiffness; and (e) improvement with exercise.[37] On the basis of the 1984 modified New York criteria, the diagnosis of AS can be made if radiological sacroiliitis (either Grade II bilaterally, or Grade III unilaterally) is present in conjunction with clinical signs (inflammatory back pain or restriction of spinal mobility).[38] However, in the absence of definite radiographic findings, one can calculate individual disease probabilities depending on the presence of typical SpA manifestations (such as inflammatory back pain, enthesitis, uveitis, asymmetric arthritis, positive family history, response to NSAIDs, HLA-B27, raised CRP). For example, the disease probability of axial SpA (early AS) in a patient with inflammatory back pain increases from 14% to around 50%–60% if there are one or two more clinical SpA features present. It further increases from 50% to 90% if HLA-B27 is positive or if the MRI is positive. Thus, in patients reaching disease probabilities of 80%–90%, the diagnosis of axial SpA should be made. The important conclusion from the probability calculations is that an early diagnosis of axial SpA can be made with sufficient probability, even in the absence of typical radiological changes.

TREATMENT

Medical professionals and experts in AS have speculated that maintaining good posture can reduce the likelihood of a fused or curved spine which occurs in a significant percentage of diagnosed persons.[39]

Medication

The major types of medications used to treat AS are pain-relievers and drugs aimed at stopping or slowing the progression of the disease. Pain-relieving drugs come in two major classes: Anti-inflammatory drugs, which include NSAIDs such as ibuprofen, phenylbutazone, diclofenac, indomethacin, naproxen, and COX-2 inhibitors, which reduce inflammation and pain. 2012 research showed that patients with elevated acute phase reactants seem to benefit most from continuous treatment with NSAIDs. Drugs used to treat the progression of the disease include: Disease-modifying antirheumatic drugs (DMARDs) such as cyclosporin, methotrexate, sulfasalazine, and corticosteroids, are used to reduce the immune system response through immunosuppression;[40,41] TNF-α blockers (antagonists), such as the biologics etanercept, infliximab, golimumab, and adalimumab, have shown good short-term effectiveness and trials are ongoing to determine their long-term effectiveness and safety.[42] Anti-IL-6 inhibitors such as Tocilizumab, currently approved for the treatment of rheumatoid arthritis,[43] and rituximab, a monoclonal antibody against CD20 is in trial.[44]

Surgery

In severe cases of AS, surgery can be an option in the form of joint replacements, particularly in the knees and hips.

Physical therapy

Some of the therapies that have been shown to benefit AS patients include: Exercise programs, either at home or supervised, are better than not having an exercise program. Group exercises are better than home exercises. Extending regular group exercises with few weeks exercising at a spa resort is better than group exercises alone. Moderate-to-high impact exercises like jogging are generally not recommended.

Prognosis

Prognosis is related to disease severity. AS can range from mild to progressively debilitating and from medically controlled to refractory. Some cases may have times of active inflammation followed by times of remission resulting in minimal disability, while others never have times of remission and have acute inflammation and pain, leading to significant disability. Over a long period of time osteoporosis of the spine may occur, causing compression and resulting in a hump. Typical signs of progressed AS are the visible formation of syndesmophytes on X-rays and abnormal bone outgrowths similar to osteophytes affecting the spine. The fusion of the vertebrae paresthesia is a complication due to the inflammation of the tissue surrounding nerves. Organs commonly affected by AS, other than the axial spine and other joints, are the heart, lungs, eyes, colon, and kidneys.[45] Owing to lung fibrosis, chest X-rays may show apical fibrosis, while pulmonary function testing may reveal a restrictive lung defect. Rare complications are cauda equina syndrome.[46,47]

Mortality

Mortality Rate is high in Ankylosing spondylitis, which is dependent mainly on the disease severity. The other factors which affect negatively are: Male gender, ESR >30 mm/hr, unresponsiveness to NSAIDs, Onset <16 years. The most common cause of death in AS is Circulatory diseases.[48,49]

CONCLUSION

AS is a complex, unpredictable disease that has puzzled and frustrated clinicians and scientists alike for centuries. It is insidious in onset, striking individuals, mostly men, at an early age, subsequently progressing over several years until structural damage manifests clinically as inflammatory back pain (sacroiliitis) and loss of spinal mobility, and a definite diagnosis of AS is made. Peripheral and extra-articular symptoms may also occur. Patients with severe AS have a reduced quality of life and loss of productivity due to work disability and sick leave. In addition, the management of AS is taxing on healthcare resources. Thus, indirect and direct costs associated with AS are high. The pathogenesis of AS is poorly understood. However, the prevailing hypothesis is that immune mediated mechanisms have a major role. Researchers are currently exploring the pathogenic role of inflammatory cellular infiltrates, including various cytokines such as TNF-α, and the interaction between the T cell response, HLA-B27, and genetic and environmental factors, including bacterial antigens.

The close relationship between AS and clinical and asymptomatic forms of IBD suggests the potential involvement of an immune reaction directed against gut bacteria. Sacroiliitis detected by radiography, MRI, or CT in the presence of clinical manifestations is diagnostic of AS. However, the presence of inflammatory back pain, plus at least two to three other typical features of SpA (for example, enthesitis, uveitis, HLA-B27 positivity, or raised ESR), is generally diagnostic of axial SpA, which usually progresses to AS over time. At present, NSAIDs, in conjunction with physical therapy, are the mainstay of treatment for patients with symptomatic AS. However, these measures are strictly palliative, and NSAIDs do not alter the course of the disease or prevent structural damage. For symptoms refractory to NSAIDs, second line treatments including corticosteroids and various DMARDs are employed. However, these treatments are of limited benefit. Emerging biological therapies target the inflammatory processes underlying AS, and thus, may favorably alter the disease process while providing relief of symptoms.

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Conflicts of interest
There are no conflicts of interest.

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