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A REVIEW ON ANKYLOSING SPONDYLITIS

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ABSTRACT

Ankylosing spondylitis is a chronic autoinflammmatory disease of the joints, belonging to the group of spondyloarthropathic disorders. The disease has a crippling effect on the axial skeleton and its progression to the later stages can have a debilitating effect on the patient. It has an under-diagnosed pathology and enigmatic pathophysiology. A strong genetic link has been found with the help of genome screening. Evidence of proinflammatory cytokines has been suggested but the unique aspect is that inflammation and structural progression are partly independent. DMARDS, NSAIDS produce symptomatic relief and anti-TNF therapy shows promising results. Current research has to delve deep into the pathophysiology for development of an ideal, curative therapy.

KEY WORDS

Ankylosing spondylitis, HLA-B27, infliximab, IL-1&IL-27,TNF-α.

INTRODUCTION

Ankylosing spondylitis(AS) is a chronic inflammatory disease involving joints and ligamentous attachments of axial skeleton[1]. It is a type of disease called spondyloarthropathies (SpA), characterised mainly by spondylitis, pauci-articular peripheral arthritis and enthesiopathy. Its occurrence is 2.7 times more common in men than in women. The average age of symptom onset is 23 (between ages 7 and 40 in >90% of cases). The commonest early symptoms are severe at rest and better during activity. Sacroilitis is the common diagnostic criteria for Ankylosing spondylitis. Asymmetric oligo-arthritis and enthesitis are common in child patients [2]. The disease has a genetic link. and various therapies and diagnostic tools have been surfaced during the unravelling of this enigmatic disease.

EPIDEMIOLOGY

The ratio of occurrence is 2.7:1 in men and women. The progression and manifestation of the disease seems to have transgender differences. Women tend to have peripheral involvement, while men have severe spinal disease. Inflammatory Bowel Disease tends to manifest itself more in women while men have psoriatic spondylitis [3].

AETIOLOGY AND PATHOPHYSIOLOGY

HEREDITY: The genetic factor has to be taken into account into discussion of Ankylosing Spondylitis marking its semblance with rheumatic disease like gout, where disease is expressed by dominant factor with 84 % penetrance in males and 12% in females[4]. According to a study, the incidence of the disease in relatives of patients is approximately 30 times than in relatives of unaffected persons. It is concluded that Ankylosing spondylitis is inherited as an autosomal dominant gene with 6 people out of 10,000 having the heterozygous constitution for the disease with penetrance of 70% for men and 10% for women[5].

HLA-B27 gene complex is supposed to confer susceptibility to the disease along with HLA-DR1. Loci on other chromosomes (1,2,9,10,16) confer additional susceptibility. Severity loci are present on chromosomes 18, 20, 21. By analysing twin pairs closely, the interaction between environmental and genes can be closely studied. The disease concordance is no more than 24% in HLA-B27 positive dizygotic twin pairs compared with 60-70% in HLA-B27 positive monozygotic twins, substantiating the role of additional genetic loci. The distribution of subtypes of HLA-B27 (now recognised to include atleast 23 subtypes, B2701-B2723), defines the occurrence of AS. Certain subtypes have protective role e.g.; HLA-B2709 appears in healthy individual in Sardinia, B-2706 is negatively associated with AS in Thai and Indonesian populations.

Another major revelation is that AS is a polygenic disease. HLA-B27 marker is a major marker but not the sole marker for the AS. Four most putative gene candidates which have the role in the AS are:

HLA-B27: This gene contributes to about 20-50% of the total genetic risk of AS. The recent meta analysis of the linkage studies showed that the strongest link occurred with the MHC region on the short arm of chromosome 6 [6].

New methods like genome screening have enabled the identification of the susceptibility genes outside the MHC of which the significant candidates are IL-1 gene cluster, ARTS-1 and IL-23 receptor gene (IL-23R) [7].

IL-1 CLUSTER: The attributable risk is estimated at 4-6% [8]. The cluster contains genes for IL-1α, IL-1βand IL-1RN. IL-1α is proinflammatory cytokine produced chiefly by activated macrophages. IL-1 over-expression in mice causes chronic proliferative arthritis [9]. Research is on for the efficiency of IL-1

inhibitor Anakinra, it is found to be effective but less compared to the effect of TNF antagonists [10-12].

ARTS 1 OR ERAP1 (Amino peptidase regulator of TNFR1 shedding): The contributable risk of developing AS is 26% [13]. ARTS-1 controls the cleavage of cytokine receptors from the cell surface and cleavage of the N-terminus of peptide precursors in the reticulum, thus ensuring that the final peptide length is sufficient for the presentation by MHC class I HLA molecules [14, 15]. Thus the loss of function of the ARTS-1 variants may produce proinflammatory effects.

IL-23R (interleukin -23 receptor): This gene links the spondyloarthropathies to chronic IBD and psoriasis. A recent study reported that Crohn's disease was associated with IL-23R gene on chromosome 1p31, a finding which was confirmed in the studies later [16, 17]. Later studies have shown that IL-23R and psoriasis are associated [18]. Several studies have time and again proved the IL-23R is one of the susceptible genes for AS [19, 20, 21]. These studies confirm and firmly establish the strong genetic predisposition to AS [22].

The role of HLA-B27 is still hazy. A plausible finding is that misfolding of the HLA-B27 molecule or formation of heavy chain homodimers has been suggested[23]. These homodimers will not be able to present antigens leading to piling up of chaperonins such as BIP (immunoglobin heavy chain binding protein) and to a stress response related to endoplasmic reticulum, which induce inflammatory factors such as IL-23. Therefore, diseases associated with HLA-B27 may be called as autoinflammmatory rather than autoimmune diseases[24]. Several reports have clued the role of IL-23/IL-17 in the pathophysiology of AS. Plasma levels are high in patients with AS but not in healthy volunteers. IL-17 levels in joint fluid are higher in reactive arthritis and undifferentiated spondyloarthropathy than in rheumatoid arthritis or osteoarthritis [25]. IL-17 has also been found in joint fluid from children with enthesitis-related arthritis[26]. Recent knowledge on pathophysiology of AS has led to development of new treatment strategy involving IL-23 blockade. It is done by human recombinant monoclonal antibody against p40I-12/23 called ustekinumab or CNTO 1275. In a randomised placebo-controlled trail in patients with Crohn's disease, the response rate was 75% in the ustekinumab arm compared to 25% in the placebo arm and with the higher dosage half the ustekinumab–treated patients achieved remission by the end of the study[27]. Controlled trials are on, for its effect on the psoriatic arthritis. The results also suggest that it may improve the joint manifestations and skin lesions. Thus, IL-23 may synchronise the pathophysiology of ankylosing spondylitis, Crohn's disease, and psoriasis[28].

ENVIRONMENTAL FACTORS: The environmental triggers remain unknown. Gram negative organisms such as Salomnella, Shigella, Campylobacter and Yersinia precipitate reactive arthropathy. Klebsilla also precipitates the above kind of arthropathy but there is no clear evidence of these things in the pathogenesis of AS.

PATHOLOGY

For a disease which is not a rarity, there is a lack of substantial pathological data that would spur the process of the drug discovery to the specific targets and produce regression of the disease. The most characteristic sites of the disease are sacro-iliac and spinal joints. These sites are inaccessible to biopsy. The normal structures do not differ much from pathological ones except during later life, which on autopsy, give only indications of end stages but not early stages of the disease. This fact is a major impedance to the complete knowledge of the histology of the AS and hence the drug discovery process. Even if data is needed, the biopsy gives a lot of discomfort to the patients. Operations on the hip and knee are often undertaken for histological study but these are questionable since the findings in the peripheral joints are not the typical of AS.

Two of the sites which can be used in the biopsy without causing much discomfort to the patients are manubrio-sternal joint and the spinous process[29]. In cases observed in the course of the disease with clinical evidence, they described an inflammatory

reaction. This is categorised as destructive phase which is characterised by inflammatory decalcification, bone resorption, destruction enclosed by a zone of reactive sclerosis. The inflammation was mostly round cell infiltration, diffuse or focal, found near vessels and ligamentous connective tissue. The cells were lymphocytes, scanty polymorphs with occasional eosinophils. The next phase is reparative phase, characterised by proliferation, ossification, and reconsruction. The reparative bone formation which follows, sometimes occur concurrently in the adjacent tissues, neither in continuity with the existing bone of the spinous process nor in between the two bones, but on the surface between it and the adjacent fatty tissue and muscle, in the same way as ossification of the intervertebral disk appears on the surface of the annulus fibrosus.

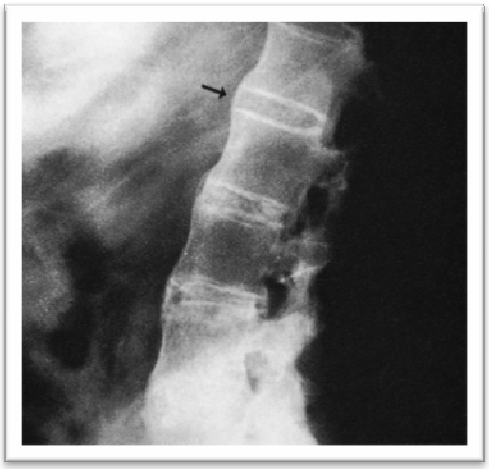

Fig 1
Image showing of Bamboo spine.

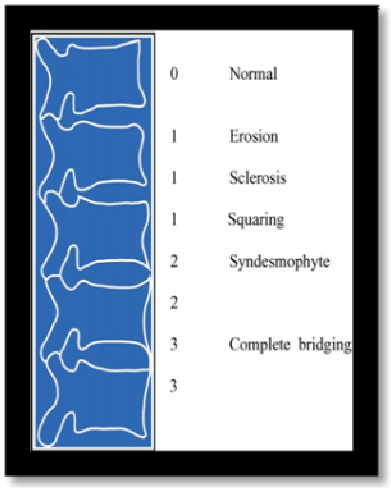

Fig 2
Image showing mSASS score

The same process occurs at manubriosternal joint. Histologically, the process is a replacement of fibrocartilage with collagenous fibrous tissue with minimal evidence of inflammation. In vertebral bodies, the bone structure reverts to normal, at later stage [29-32]. The characteristic transformation occurs in the intervertebral disks, the peripheral fibres of annulus fibrosus spreading from margin of epiphysial ring of the vertebral body on either side and meeting in the middle, this produces a 'beaking phenomenon' which later develops into 'bamboo spine'(depicted in Fig.1). An advanced phase of chondroid metaplasia in the annulus fibres before ossification occurs, but no true inflammation is seen. These data support the role of inflammation as a trigger of an ossification process that becomes partly independent from inflammation. When peripheral joints are involved, there is tendency towards ankylosis. Fibrous adhesions form early and movement causes haemorrhage and siderosis of tissues. The characteristic endarteritis obliterans tend to occur. The structural progression of AS is slow and irregular and shows significant interindividual variations. The modified Stokes Spinal Score (mSASS depicted in Fig.2) is a validated tool to assess the axial structure damage. This score is a chief measure of ossification rather than overall radiological progression[33]. Few factors predicting disease progression have been identified. The only predictive factor found consistently in the epidemiological studies is the existence of pre-existing syndesmophytes[34]. Even measuring the inflammation does not give true picture of the disease since it is weakly correlated to structural progression. Structural progression involves the formation of new bone which is stabilising and reparative response to inflammatory and mechanical stress[35]. The bone formation is inramembranous, endochondral and

chondroidal, without cellular hypertrophy or local hypervascularity[36].

CLINICAL FEATURES

The major clinical features of the ankylosing spondylitis are:

- Insidious onset of discomfort
- Age at onset is <40 years
- Morning stiffness
- Persistence of symptoms for >3 months
- Improvement with exercise

Other clinical features are:

- Sacroilitis
- Achilles tendonitis
- IBD
- Cauda equina syndrome
- Pleuritic type pain
- Aortitis/conduction defects
- Upper lobe pulmonary fibrosis
- Stiff neck
- Iritis
- Scalp psoriasis
- Temporamandibular arthropathy
- Kyphosis
- Chest wall pain
- Osteoporosis
- Spondylodiscitis
- Weight loss
- Peripheral arthritis(occurs mostly in women)
- Minimal trauma causes fractures
- Amyloidosis

One of the features of the ankylosing spondylitis is that it does not die out. It continues to remain active. Flares occur, but their pathogenesis remains unclear. Fatigue is the major component of the disease and it is difficult to manage than pain and stiffness. No system in the body is specifically affected.

DIAGNOSTIC CRITERIA

There is no set of standard diagnostic criteria for AS. Sacroilitis, stiffness, positive familial history and radiological data are the most common indicators. Some of the criteria which is being followed around the world as follows:

- Newyork criteria:
  - limited movement of lumbar spine in three planes
  - Pain in lumbar spine or at dorsolumbar junction
  - Chest expansion<2.5 cm
- Radiological criteria:
  - Unilateral sacroilitis grade III-IV or bilateral sacroilitis grade I
- European spondyloarthropathy study group diagnostic criteria :
  - Inflammatory spinal pain or synovitis(asymmetrical or predominantly in the lower limbs) and one of the following:
  - Positive familial history
  - Psoriasis
  - IBD
  - Buttock pain
  - Enthesopathy
  - Sacroilitis

Laboratory tests regarding ESR, serum IgA, serum creatinine phoshokinase and alkaline phosphatise give only partial picture of the disease. The clinical status of the AS can be defined in terms of metrology.
BASMI→ Bath Ankylosing Spondylitis Metrology Index
BASFI→ gives the expression of function
BASDAI→an index of disease activity
BAS-G→ gives the global status
BASRI→ gives the radiological index.

MANAGMENT AND THERAPY

There is no well established curative therapy, but therapies do exist to give a symptomatic relief to

- o Reduce inflammation
- o Relieve pain
- o Maintain good posture and function

The common approach is the patient and familial counselling. Most of the patients are HLA-B27 positive. The risk of transmitting it to children is 50% and the children have 1/3 risk of developing the AS. Thus the overall risk is 1/6. Smoking should be avoided. General fitness and swimming should be encouraged. Physiotherapy has a major role. Patients are instructed in dry land and hydrotherapy exercise program. NSAIDS are indicated. They are used to relieve pain and to reduce inflammation. Indomethacin is well accepted.

Cox-2 specific inhibitors like rofecoxib and celecoxib is appropriate for those who cannot tolerate conventional NSAID therapy. DMARDS like corticosteroids, gold, pencillamine have no role in AS. Sulfasalazine has an effect on the peripheral arthritis. The same is the case with methotrexate.

Biphosphonates have an impact on the underlying osteoporosis and infectious disease itself. It may also have an effect of spinal symptoms. Pulsed intravenous corticosteroids such as methylpredinosolone may be used in severe disease. Anti-TNF therapy with *infliximab* or *etarnecept* produces significant results. This therapy is being increasingly accepted around the world backed by the support of the clinical trial results. Surgical intervention is the solution at later stages of the disease with total hip replacement is excellent at 20 year follow up. In cases with severe spinal curvature, spinal osteotomy is undertaken[37].

NEW THERAPEUTIC TARGETS

Therapy for AS mainly revolve around the inflammatory mediators and their modulation. The two inflammatory mediators involved are interleukins and TNF-α. Their levels are increased in the diseased condition. Modulation of their levels is important in controlling the severity and progression of the disease. Anti-TNFα therapy with infliximab and etarnecept is an established therapy with 75% of the patients showing improved clinical condition[38]. Further, clinical trials are on in the above drugs regarding the safety o the chronic therapy of the drug. Il-1 could be a new target. Drugs controlling the IL-1 levels in the blood could have a beneficial role. An IL-1 inhibitor Anakinra is used but the effect was small compared to that of TNF antagonists[39].

Extracellular inhibitors seem to have little influence on the effects of IL-1α.the research is being focussed on the intracellular activity of IL-1 and its proinflammatory effects. A new treatment strategy involves IL-23 blockade. Ustekinumab is an IL-23 inhibitor. It has shown good improvement in the Crohn's disease. So it is rational to use it in the AS treatment since AS and Crohn's disease being closely related. Studies have shown that IL-17 levels are higher in reactive arthritis and undifferentiated spondyloarthropathies than in rheumatoid arthritis and osteoarthritis. So IL-17 inhibitors can be a possible treatment. Since organisms like Klebsiella are implicated in some cases, to a lesser extent, less starch diet could be a rational, add on therapy. Another therapy used for temporary management is deep X-ray therapy[40].

CONCLUSION

Ankylosing Spondylitis belongs to a group of enigmatic diseases which do not have ideal, curative therapies. The disease progression still baffles many pathologists and radiologists. For different reasons such as strong familial tendency and the disease tends to manifests at points which are not easily accessible to radiology, there is no substantial pathological data to understand the disease completely. It shares similarities with other diseases such as Rheumatoid arthritis, Reactive arthritis, Crohn's disease but it is quite unique. Specific drug targets are lacking, anti TNF therapy provides a dramatic benefit but it is not an ideal treatment. The safety of the TNF therapy on chronic usage is under clinical study. That the course of AS progression itself is not well elucidated it would be irrational and unsafe to consider anti-TNF therapy ideal in the long run.

Another characteristic aspect of AS is that the evidence of inflammation is minimal at most characteristic sites and the repair by ossification. The most interesting point of AS is that the inflammation which comes in the first phase of the disease is the trigger for the reparative process which is the next phase of the disease process and it is surprising to note that the current drug targets focus to decrease the inflammation which may impede the ossification process. Even the new animal models, such as transgenic rats, are not ideal for pre-clinical AS study since AS developed in the rats is quite different from the AS in humans regarding the histological changes in the intervertebral disks. Since the exact radio-pathology of AS is *terra incognita*, for the future, there should be an immense collaboration between radiology and pathology. Since the actual sites of diseases

are quite difficult to access, the radiologist must guide the pathologist to the actual site which will allow greater exploration and understanding of the histological, structural, biochemical aspects of the disease which is important for progress of research. Unless we have a hard radio-pathological data we cannot elucidate the disease and distinguish it from other forms of the disease such as tuberculous and pyogenic types.

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