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Mini-Review

A Mini-Review on Ankylosing Spondylitis (AS): An Uncommon Disease

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ABSTRACT

Ankylosing Spondylitis (AS) is an aberrant inflammatory chronic disorder characterized by an inflammation to joint particularly vertebrae of spine potentially instigates them to inter-fuse. This disease is also well known as Bekhtrev disease, Bechterew's disease or marie-strumpell disease. Symptoms such as pulmonary fibrosis, restrictive lung disease, aortitis often occur rarely and these are often misdiagnosed with some other disease condition. Although recent research and genomic studies suggests that there were many etiological factors that contributed to this disease onset and progression. Among these it's association with *HLA B-27* gene is widely researched one or established one. Several genomic studies had also revealed the association of innate immunity with ankylosing spondylitis while other studies define *K. pneumoniae* infection as a perpetuating factor in AS. However this association has not been fully understood. One of the interesting mechanism by which this disease progress is the co-stimulation of TNF and IL-17 (interlukin-17) and the involvement of *SOX*9^{+}ve (SRY Box Transcription Factor 9^{+}ve). The probability of occurrence of *HLA-B27* gene in general population is (~8%).

Keywords: Aberrant, *HLA B-27*, *Klebisella pneumoniae*, Enthesitis, Uveitis, Schober's test

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INTRODUCTION

Ankylosing Spondylitis (AS) is an aberrant inflammatory chronic disorder characterized by inflammation to joints, particularly vertebrae of the spine potentially instigating them to inter-fuse (Walker J, 2006; Breban M, 2005). This condition was first described by Bernard Connor in the 1600s. However, its adequate description was first provided by Vladimir Mikhailovich Bekhtrev (Russia) in 1893, Adolf Strumpell (Germany) in 1897, and Pierre-Marie (France) in 1898 which further served to be a foundation step contributing to its precise diagnosis. That's why this disease is also well known as Bekhtrev disease, Bechterew's disease, or Marie-strumpell disease (Thiery M, 2012; Strümpell A, 1897; Bogousslavsky J, 2011).

Several studies associate that men are 2-3 times more afflicted to this estate than women (Shahlaee A, *et al*., 2015). Although there are many etiological factors governing this disease progression however genetic etiology was determined to be the most probable root (Akgül O and Ozgoçmen S, 2013). AS cases vary from mild to severe forms and often expands the patient's demisal probability when the inflammation occurs to vital organs or previous circulatory disorder (Bakland G, *et al*., 2011).

Epidemiology

The recent research studies have revealed that the progression of AS is more common (i.e. ~2-3 times) in males than in females (Sieper J and Poddubnyy D, 2017; Eashwar VA, *et al*., 2016). Based on a combined study done (from thirty-six eligible shortlisted studies) by taking mean prevalence of AS cases in a general population of 10000 individuals.

It was observed that highest percentage of individuals affected with this condition were from North America (~31.9) followed by (~23.8) in Europe. In Asia and in Latin America, it was (~16.7), (~10.2) respectively. Similarly it was comparatively less (~7.4) in Africa (Dean LE, *et al*., 2014).

Etiology

Although recent research suggests that many etiological factors contributed to this disease's onset and progression, none among them had been established to be a key factor. The etiology of this disease can be investigated further by classifying them as-

- Autoimmune effects
- Genetic factors
- Microbial attack
- Miscellaneous

LITERATURE REVIEW

Pathogenesis

Recent advanced studies suggest that over 90% of people with rheumatoid arthritis developed cervical spondylitis (Akhondi H and Varacallo M, 2022).

Association with microbial infection

Many reports suggest a potential link between *Klebsiella pneumoniae* infection and AS. These studies define *K. pneumoniae* infection as a perpetuating factor in AS. However, this association has not been fully understood. *K. pneumoniae* is a gram-negative bacteria that has a large genome of plasmids and chromosomal gene loci. This genome provides the ability of hypervirulence and multi-drug resistance to the different strains of these bacteria (Zhang L, *et al*., 2018; Martin RM and Bachman MA, 2018). The research was done on an 84 years old female patient with persistent lumbar back pain. She had lumbar spine tenderness and her inflammatory markers were elevated. MRI showed L4-L5 spondylodiscitis and bacterial examination which suggested the presence of *K. pneumoniae*. In another separate research, CT scan was done on a 90 years old male who had undergone sigmoidectomy and who had been given antimicrobial treatment. He was re-admitted with a complaint of fever. CT scan revealed that he had spondylodiscitis and inflammation in the 8th and 9th thoracic vertebrae. When his blood sample was examined, it was positive for the presence of *K. pneumoniae* (Filipe A, *et al*., 2012; Inagaki A, *et al*., 2019). Similarly, spondylitis and osteolytic proliferative bone lesions were also observed in a pet lizard infected with *K. pneumoniae* which was identified by taking a small amount of material from spinal swelling. Information was collected from

various databases (PubMed, Embase, Medline, Web of Science and scopes) with 25 case-control-based studies. All these findings suggested a strong association between elevated serum IgA, IgG and *K. pneumoniae*. However much research is still required to prove this link (Vetere A, *et al*., 2021; Long F, *et al*., 2022).

Association with HLA B-27 *gene*

The probability of occurrence of the *HLA-B27* gene in the general population is ~8%. However, the contribution of this gene as an etiological factor in the progression of this disease is ~90%. This class of gene exhibits a high degree of polymorphism (~160 different types). This not only influences its specificity towards binding to an antigen but also contributes significantly to its severity and pathogenesis. AS is a highly heritable type of arthritis. *HLA-B27* allele as mentioned above has a strong tendency to cause AS. When a cross-sectional study was done on 70 patients with AS by the department of rheumatology of BSMMD, this study concluded that almost seventy-seven percent of individuals were *HLA-B27* positive. Some patients who were positive for this allele exhibited symptoms like uveitis, enthesitis and tendinitis. Though HLA allele is said to be associated with more than ~100 diseases, but for many of them, the mechanism of action is largely unknown or not well established (Mekhola MH, *et al*., 2019; Asquith M, *et al*., 2019). Enthesitis is the major concern associated with AS. Enthesitis can be defined as a condition where a ligament or bone connects to bone and undergoes calcification. Bone marrow and Mesenchymal Stem Cell (MSC) samples were collected from the hip around the facet joint. For a person having AS, it suggested that genetic *HLA-B27*/Retinoic Acid Receptor Beta (RARB)/Tissue Non-Specific Alkaline Phosphate (TNAP) be associated with calcification of ligaments and tendons surrounding vertebrae (Liu CH, *et al*., 2019). Other mechanism to be involved in enthesitis is Tumor Necrosis Factor (TNF) induced Dickkopf-1 (DKK1) expression. NF-kB alone downregulated DKK1. While NF-kB along with TNF upregulated and induced DKK1 expression ultimately leading to unwanted boy mass formation. The other interesting mechanism is the costimulation of TNF and IL-17 (interlukin-17) and the involvement of SOX9^{+}ve (SRY-Box Transcription Factor 9^{+}ve), which led to the secretion of osteocalcin followed by mineralisation and calcification (Jo S, *et al*., 2021; Jo S, *et al*., 2022).

Role of innate immunity

Several genomic studies have revealed the association of innate immunity with ankylosing spondylitis (Vanaki N, *et al*., 2018). Based on the data collected from various studies, the association of extracellular and intracellular Pattern Recognition Receptors (PRRs) like Toll-Like Receptors (TLR) and AS has been established. In some cases AS presented with an infection of microbes, there is an activation of TLRs which activates innate immunity and causes inflammation. However, there had also been past studies done suggesting TLR's role in autoimmunity.

DISCUSSION

Symptoms

This condition belongs to the seronegative spondylopathy class. AS has been observed to exhibit a wide variety of clinical symptoms and some of them are mentioned below-

Systemic symptoms (weight loss, fatigue): These types of symptoms are pretty common and may be due to a variety of etiological factors that may include pathological or physiological conditions. However, these conditions hinder the correct prognosis.

Chest pain: In research conducted involving 45 patients with AS, 25 of them or (~55.56%) exhibited signs of chest pain which also involved a lower chest expansion than the usual. Also, chest pain in 8 patients (~17.7%) developed early. So, it can be said that AS exhibits a more frequent symptom i.e. chest pain.

Enthesitis: The occurrence of this symptom has already been discussed in the pathogenesis heading.

Anaemia: Out of research conducted in Ukraine, the occurrence of anaemia as a symptom was observed in ~28.8% of cases. However, its severity depends on the stage of the current anaemic syndrome. It is one of the most common extra articular symptoms observed among patients with AS.

Acute Anterior Uveitis (AAU): From a statistical analysis published it was found that in most cases this symptom often occurs usually after (TNFi) TNF inhibitors intake. However, this symptom has genetic as well as microbiome predisposition. Other symptoms such as pulmonary fibrosis, restrictive lung disease, and aortitis often occur rarely and these are often misdiagnosed with some other disease condition.

Diagnosis

- Schober's
- Inflammatory marker (CRP and ESR)
- Genetic test (HLA B27)
- X-ray (spine, sacrum)
- MRI of spine

Treatments

TNF-alpha antagonist: TNF -alpha antagonistic drugs such as Etanercept and Infliximab are currently widely used to manage the AS condition. These drugs are accounted for their rapid onset combined with their consistent effectiveness against axial and peripheral ankylosing spondylitis. They have been shown to reduce inflammation and abolish any activity of TNF-alpha (Jo S, *et al*., 2021; Clegg DO, 2006).

IL-17 inhibitors/IL-17 antagonists: These are now the most commonly used class of drugs, thus emerging as a new treatment option. Several scientific data provides the evidence about efficacy and stability of these drugs. Secukinumab (anti-IL-17A) is the most widely used drug involved in treating AS (Yin Y, *et al*., 2020; Wendling D, *et al*., 2019).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): This class of drugs is commonly used for their action on inflammation. However, they provide symptomatic relief. Research suggests that there was a reduction in the amount of Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP) and Immunoglobulin A (IgA) levels when individuals were provided with NSAIDs drugs. It was also observed that reduction in other inflammatory mediators like IL-6, IL-12 and TNF-α. However, NSAIDs are known to cause GI toxicity (Fan M, *et al*., 2020; Yan Y, *et al*., 2018).

Physical therapy and exercise: Exercise and physical therapy combined with drugs have shown to greatly improve symptoms and contribute to a better quality of life. Physical therapy such as hydrotherapy, hot water treatment and ultrasound combined with flexibility exercise improve the body condition which was damaged due to axial spondylitis (Dawes PT, *et al*., 1988; Brüner M, *et al*., 2021; Zviahina OV, *et al*., 2020; Shevchuk S and Zviahina O, 2019; Ahn SM, *et al*., 2022; Rosenbaum JT and Asquith M, 2018; Sun P, *et al*., 2019).

CONCLUSION

The lack of treatment options in relation to AS is associated with our incomplete understanding of the causative pathogen role and the absence of biomarkers. Although recent improvements in science and clinical studies have suggested a few of the treatment options available, there is no effective cure for this condition but drugs combined with exercise can relieve the pain. The study findings found the association with *HLA B-27* gene in pathogenesis and denote an association of elevated serum IgA, IgG with *K. pneumoniae* and much more research is still required to prove this more

evidently.

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