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A Brief Review on Spondylitis; The Problems of Inflammatory Diseases.

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ABSTRACT

Chronic inflammatory diseases of arthritis are termed as spondyloarthropathies, which mainly affects the joints of the spine and sacroiliac region. The sacroiliac region includes the pelvis and lower spine area of human body. The widespread inflammation due to spondylitis are sometimes known to affect the other organ system of human body. Ankylosing spondylitis (AS) is a subcategory of spondyloarthropathies that leads to inflammatory rheumatic disease involving primarily the sacroiliac joints and the axial skeleton. The major clinical observation are progressive stiffness of spine with back pain. Oligoarthritis causes stiffness and inflammation of the hips and shoulders area along with enthesopathy, and anterior uveitis with involvement of the heart and lungs that are also observed in some cases.

This article provides a brief overview on spondylitis and its various effects imparted on the affected patients, along with discussion on symptoms, causes, diagnosis, and the effect of treatment provided to these subjects as mentioned in the studies listed in this article. The studies performed on patients that were differentiated in terms of age groups, sexual orientation, region of habitat, food, and addictive habits, working conditions involving excessive fatigue and shock, childbirth in women's, family history of spondylitis and Iritis conditions.

Keywords: Spondylarthritis, Spondylitis, Oligoarthritis, Ankylosing spondylitis, Chronic Inflammatory Diseases, Sacroiliac Joints.

Introduction

The word Spondylitis represents a group of chronic arthritis-type diseases, mainly affecting the joints of the spine and sacroiliac region, this includes involvement of the axial skeleton that causes inflammation of sacroiliac joints and spine, large joints, fingers, and toes that results in stiffness and pain[1]. Other conditions such as peripheral arthritis, enthesitis, dactylitis, acute anterior uveitis, associated psoriasis or inflammatory bowel disease, and presence of the HLA-B27 antigen are also known to be associated with spondylarthritis conditions.

Spondylarthritis (SpA) are generally classified as axial SpA or peripheral SpA. The axial SpA involves spine and sacroiliac joints, that leads to whereas peripheral SpA involves, peripheral arthritis, enthesitis, and dactylitis[2-5]. The non-radiographic axial spondylarthritis is form of arthritis where erosive damage to the sacroiliac joints are not substantial[6].Psoriatic arthritis is found among people with conditions of psoriasis. Psoriasis is a disease condition that causes red patches on the skin with silvery scales, most patients develop psoriatic arthritis condition on very later stages of development of the Psoriasis disease condition. Joint pain, stiffness and swelling are the main signs and symptoms of psoriatic arthritis[7].Reactive arthritis condition is triggered by infection caused by other part of the body, most often it involves infection of intestines, genitals, or urinary tract. Knees, ankles and feet are the main target points in this infection conditions and sometimes also affects skin, eyes and urethra, this infection condition is also known as Reiter's syndrome[8]. Enteropathic arthritis (EnA) occurs with conditions of inflammatory bowel disease (IBD) that involves chronic inflammation of all or part of your digestive tract. This condition is also known as enteropathic arthropathy and the Arthritis is caused by such conditions leading to swelling and pain in the joints[9].Ankylosing spondylitis is a type of arthritis that causes inflammation in the joints and ligaments of the spine. It may also affect peripheral joints like the knees, ankles, and hips. Normally, the joints and ligaments in the spine help us move and bend[10].

The following figure is a Venn diagram representing the spectrum of interconnection of various forms of spondylarthritis.

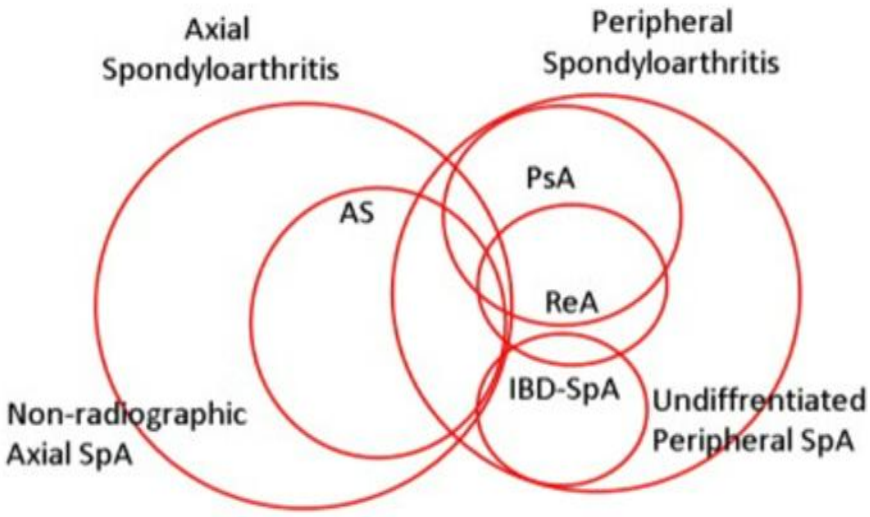

Figure 1: Venn diagram showing the spectrum of Spondylarthritis. AS – ankylosing spondylitis. PsA – psoriatic arthritis. ReA – reactive arthritis. IBD-SpA – inflammatory bowel disease associated arthritis. (Figure reproduced from the article written by Siba P. Raychaudhuri, Atul Deodhar, the classification and diagnostic criteria of ankylosing spondylitis, published in Journal of Autoimmunity, Volumes 48–49, February–March 2014, Pages 128-133

Ankylosing spondylitis and HLA-B27 gene correlation

K. Yaseen described Ankylosing spondylitis is 3 times more common among men than women[11], developing most commonly between the ages of 20 and 40. The cause of ankylosing spondylitis is not known, but the disease tends to run in families, indicating that genetics plays a role. Ankylosing spondylitis is 10 to 20 times more common among people whose parents or siblings have it. The HLA-B27 gene is present in 90% of white people who have ankylosing spondylitis, but it is also present in up to 10% of the general population depending on ethnicity. However, having the HLA-B27 gene does not mean that a person has or will develop ankylosing spondylitis. For example, only 50% of identical twins both have the disorder, which suggests that unknown environmental factors also may be involved.

Ankylosing spondylitis case studies

N. Simpson et. al, presented an analysis of 200 cases of ankylosing spondylitis, together with a review of some ideas on the disease[12]. Data were obtained from the hospital notes of cases admitted to the Royal National Hospital for Rheumatic Diseases, Bath, during the period 1938-48. This study has been performed on the basis of Sex incidence, Age of Onlet and other Number of associate factors related to be Sepsi, Trauma. Exposure to excessive fatigue and shock, childbirth, family History, occupations, Iritis,

Ankylosing spondylitis patients and fecal calprotectin level assessment.

R. Klingberg et al, indirectly investigated the prevalence of intestinal inflammation caused in ankylosing spondylitis patients by assessing the levels of fecal calprotectin[13]. This serum levels were correlated with the calprotectin concentration of calprotectin in feces with reported gastrointestinal symptoms, medication, and measures of disease activity. Patients with ankylosing spondylitis were invited at the study centers and physical examinations was performed, including back mobility tests. Samples of stools and blood were collected and analyzed for fecal and serum calprotectin. The findings were Elevated levels of fecal calprotectin (>50 mg/kg) in 140 of 205 AS patients (68%). Levels of fecal calprotectin that were associated with increasing age, disease duration, ESR, CRP, and serum calprotectin. Study conducted suggested that the fecal calprotectin could be used as a marker for subclinical intestinal inflammation in AS and should be measured after stopping NSAIDs, but further endoscopic studies are also recommended.

Ankylosing spondylitis susceptibility to human leukocyte antigen B27 (HLA-B27)

E. Dakwar et al, produced a review explaining the main clinical features to be back pain and progressive stiffness of the spine[14]. Strong association between human leukocyte antigen B27 (HLA-B27) and susceptibility to Ankylosing spondylitis were reported over the past 30 years. The authors presented detailed review pertaining to the pathogenesis of Ankylosing spondylitis over the past several decades and its correlation with HLA-B27 playing a critical causative role in its pathogenesis.

Figure 2: Radiographs showing examples of Grade II (A), Grade III (B), and Grade IV sacroiliitis (C) (Figure reproduced from the review article written by ELIAS DAKWAR et al, published in Neurosurg Focus 24 (1):E2, 2008).

Diagnostic delays in spondylarthritis and identification factor relevance.

M. Mboussi et al, presented a detailed study on the diagnostic delay in spondylarthritis and identify factors associated with it[15]. This study included about 276 patients: 146 males (53%) and 130 females (47%) with a sex ratio of 1.1 and the mean age at the diagnostic were kept to be 38.87 years. The Comorbidities included subjects with smoking (33 patients), cardiopathy (3 patients), hypertension (19 patients), diabetes (14 patients) and peptic ulcer (5 patients). The duration of symptoms was 2.6 years, and average diagnostic delay was 6.5 years with a median of 2.1 years. In univariable and multivariable linear regression analysis, low socio-economic level (p =0.023) and low educational level (p=0.042) were statistically significant parameters associated with a delayed diagnosis.

C-reactive protein/albumin ratio correlation with the Bath Ankylosing Spondylitis Disease Activity Index score

Z. Ammor et al, studied 112 patient and established relationship between the value of C-reactive protein/albumin ratio (CAR), platelet ratio[16], neutrophil lymphocyte ratio, and Bath Ankylosing Spondylitis Disease Activity Index score and emphasized that CAR can be used as a practical measurement tool for following up of patients with axial spondylarthritis axial spondylarthritis because it can be used quickly under routine ambulatory conditions, in correlation with the BASDAI

Study of Single nucleotide polymorphism

Y. Zhang et al, Selected a total of 70 independent single nucleotide polymorphism subjects as instrument variables in the MR analysis of total WBC[17]. Higher leukocyte counts were found to be associated with a higher risk of rheumatoid arthritis by the IVW method study selected single nucleotide polymorphism (SNPs) associated ($p<5e-8$) with exposure (LC) from a genome-wide association study (GWAS). This study indicated the insidious causation between LC and the risk of rheumatoid arthritis.

Quality-of-life indicators using the SF-36 questionnaire.

O. Pavliuk et al, investigated the quality-of-life indicators using the SF-36 questionnaire in men with ankylosing spondylitis and its correlation for assessing their relationship with the structural and functional state of the bone tissue[18]. This study illustrated about the correlation of the SF-36 questionnaire with patients of ankylosing spondylitis that had significantly lower indicators of both physical (37,3 $\pm$ 1,5 points) and mental (44,2 $\pm$ 1,7 points) components of health in comparison with the control group (99,1$\pm$ 0,3; 97,4$\pm$ 0,7 points, respectively).

Establishment of patterns and treatments of noninfectious uveitis

P. Triggianese et al, developed studies to establish patterns and treatments of noninfectious uveitis from a population-based single-center study carried out in a Tertiary Referral Rheumatologic Clinic in Italy[19]. This study concluded with 100 patients representative estimate of extent and patterns of noninfectious uveitis in an Italian adult cohort from a single Rheumatologic Clinic and documented that Rheumatologic referral might dramatically impact treatment strategies in noninfectious uveitis.

Ankylosing spondylitis and its traceability in history

S. Murphy et al, in a descriptive review illustrated About history of Ankylosing spondylitis and its traceability as far back as in ancient Egypt with evidenced by the discovery of its presence in ancient Egyptian mummies to the late 20th century[20], The inheritance nature of Ankylosing spondylitis has proven link to a genetic factor, HLA-B27. Each discovery that was made throughout the years led to further investigations into the pathophysiology, diagnosis, and treatment of Ankylosing spondylitis. In the new era the diagnostic criteria for AS have undergone series of changes before the present-day diagnostic criteria for AS were ultimately determined in 2009 by the Assessment of Spondylarthritis International Society.

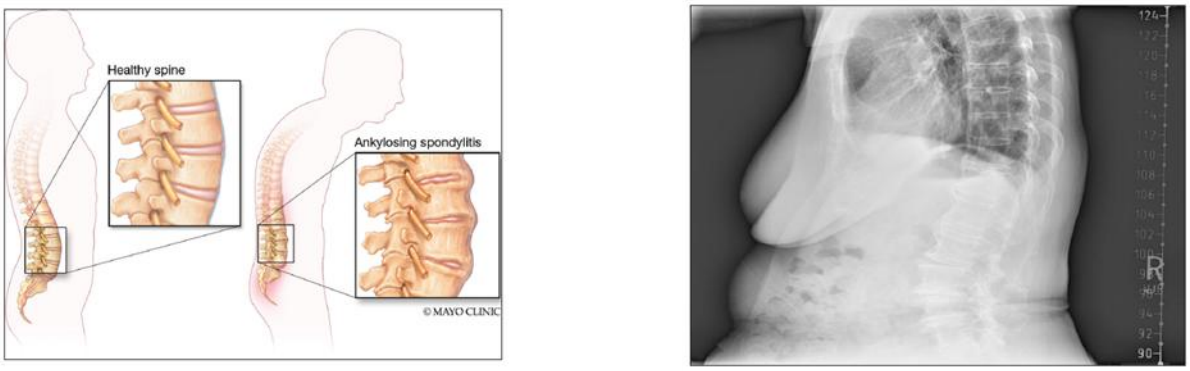

Figure 3: Depiction of ossification of vertebral ligaments leading to fusion of vertebral segments and significant increase of overall kyphosis. (left) and X-ray imaging of patient with AS and the pathognomonic "bamboo spine." (right), (Figure reproduced from the review article written by Sierra N. Murphy et al, published in Surgical Neurology International • 2022 • 13(297).

Fecal microbiota composition by using GA-map™ Dysbiosis test.

K. Klingberg et al, assessed Fecal microbiota composition by using GA-map™ Dysbiosis test that reported the degree of deviation of the microbiota composition compared with healthy control population by suing Dysbiosis Index (DI) [21] score from 1-5. The differed observation of the fecal microbiota composition between patients with normal (≤ 50 mg/kg, n = 57) and increased (≥200 mg/kg, n = 36) fecal calprotectin. Patients with increased fecal calprotectin had lower abundance of bacteria with anti-inflammatory properties such as Faecalibacterium prausnitzii and clostridium and higher abundance of the genus streptococcus.

Sex-specific predictors of spinal radiograph.

Anna Deminger et al, performed longitudinal study, with Swedish patients with AS, age (mean ± SD) 50 ± 13 years. Among the group of 204 patients the progression of sex-specific predictors of spinal radiographic showed that predictors may partly differ between the sexes[22]. Furthermore, new predictors identified were obesity in both sexes and exposure to bisphosphonates in women's. Among previously known predictors, baseline AS-related spinal radiographic alterations predicted radiographic progression in both sexes, high CRP was a predictor in men (with a trend in women) and smoking was a predictor only in men were established.

Hematological testing and radiographic examination

Huanhuan Jia et al, performed hematological testing, radiographic examination, family aggregation analysis, pathological analysis, and genetic testing on a group of cynomolgus monkeys having joint lesions reported of spinal stiffness over a period of 2 years[23]. The obtained results confirmed that the animals under diseased conditions suffered from spontaneous ankylosing spondylitis manifested by pathological changes and biochemical indicators similar to that of ankylosing spondylitis human patients. This study was offered as an excellent substitute of preclinical research.

Ankylosing Spondylitis and its etiology

Wei Zhu et al, presented a review article in bone research on Ankylosing Spondylitis, and details about its etiology, pathogenesis, treatment, and bone research. In this study chronic inflammatory autoimmune disease and its effect on the spine joints and chronic pain are corelated[24]. The importance of Immune cells and innate cytokines has been suggested in the pathogenesis of Ankylosing Spondylitis, especially human leukocyte antigen (HLA) B27 and the interleukin 23/17 axis.

Potential biomarker for early detection of Ankylosing spondylitis

Wenxin Gao et al, presented identification of the early potential biomarker related to the immunity response to Ankylosing spondylitis, furthermore a predictive risk model to identify differentially expressed genes with improving diagnostic and therapeutic efficiency has been done on the basis of Gene Expression Omnibus and database (GEO) [25]. A gene co-expression network between AS and healthy samples has been presented.

Patient acceptable symptom state in patients of Ankylosing spondylitis

G. Wariaghli et al, made a 4-week prospective study with 200 patients of Ankylosing spondylitis. Patient Acceptable Symptom State (Pass) was defined as the value beyond which the patients consider themselves as well [26]. The pass was estimated on patients on the two-time durations of 2 and 4 weeks, the outcomes were measured on a visual analogue scale such as BASDAI and BASFI tool, these tools are generally used for measurement of the

disease activity of ankylosing spondylitis, as it contains six questions about the symptom such as fatigue, pain and stiffness in the score range of 0 to 10. An anchoring method was used to determine the current condition is satisfactory or not.

Management of ankylosing spondylitis as per international working group

J Zochling et al, taken a task for establishing evidence-based recommendations for the management of ankylosing spondylitis, this effort was for 'Assessment in Ankylosing Spondylitis as per international working group and the European League Against Rheumatism27. The final considered recommendations were the use of conventional method of treatment with non-steroidal anti-inflammatory drugs, antirheumatic drugs, treatments with biological agents, simple analgesics, local and systemic steroids, non-pharmacological treatment (including education, exercise, and physiotherapy), and surgical interventions. The final conclusion involved ten key recommendations for the treatment of AS were developed and assessed using a combination of research-based evidence and expert consensus.

Phase III studies of MSB11022 at Merck Darmstadt, Germany

Scientist at Merck research and development facility work hard to discover and develop various technologies that could ease the life of patients. With new discoveries in the field of medicines and vaccines "Merck" understands and help fight some of the world's most serious health concerns that are critical along with contributing gestures for respecting and giving honor to the life of patient communities. In zeal for further achievements in the healthcare division of Merck includes Merck Biosimilars, Merck Biopharma, Consumer Health, and Allergopharma. The facility is situated in Canton de Vaud, Switzerland, near Merck's cutting-edge biologics production facilities in Aubonne and Corsier sur Vevey, with assistance from other business locations throughout Europe. Using both internal biologics research and development capabilities and collaborations with other biosimilar companies, Merck Biosimilars is building a portfolio of biosimilars targeted at inflammatory and oncological conditions.

The latest move in the Excel direction of helping to make patients' lives easier, Merck has initiated the phase III studies of MSB11022. In phase I study MSB11022 has demonstrated bioequivalence and comparable safety and immunogenicity profiles on a group of healthy volunteers. The phase III study of MSB11022 which is a proposed biosimilar of adalimumab, used to treat moderate to severe conditions of chronic plaque psoriasis[28] is a commitment for delivering high-quality biologics to patients all over the world.

Adalimumab a recombinant human monoclonal antibody that binds specifically to tumor necrosis factor-alpha (TNF-α), blocking interaction with its cell surface receptors and thereby reducing the impact of inflammation. Humira® (adalimumab) is approved for use in a range of chronic inflammatory conditions such as psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, Crohn's disease and juvenile idiopathic arthritis. MSB11022 a proposed biosimilar of Humira® has been developed as a high quality biosimilar of adalimumab in the Swiss facilities of Merck using the most advanced analytical methods. Adalimumab is a biologic therapy used in the treatment of several chronic conditions including plaque psoriasis, Crohn's disease, ulcerative colitis, juvenile idiopathic arthritis, psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis.

Conclusion:

In past many years spondylarthritis has been a world-wide problem, imparting severs consequences on patients physical and financial health. In recent years important steps toward predetermining the presence and progression of this disease through various bioanalytical methods came into picture. These are many patient centric studies performed throughout the globe to understand and tackle this problem better with patients different age group, sex, food habits and different area are preformed The scientific and the moral support provided to these patients from many scientific groups came into light with emergence of more modern technologies that could treat this disease better, along with keeping these technologies at the affordable prices to support the financial wellbeing of the patients.

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