"A STUDY ON CLINICAL PROFILE AND OUTCOME OF UNDIFFERENTIATED SPONDYLOARTHROPATHY"

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CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY ON CLINICAL PROFILE AND OUTCOME OF UNDIFFERENTIATED SPONDYLOARTHROPATHY"** presented here is original work done by **Dr.I.VENKATESH**, DM Post Graduate in the Department of Rheumatology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai- 600 003 in partial fulfillment of the university rules and regulation for the award of D.M.Branch IX- Rheumatology, under my guidance and supervision during the academic period from 2009-2012.

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DECLARATION

I, **Dr.I.VENKATESH** hereby solemnly declare that this dissertation entitled **"A STUDY ON CLINICAL PROFILE AND OUTCOME OF UNDIFFERENTIATED SPONDYLOARTHROPATHY"** was done by me in the Department of Rheumatology, Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai-3 during February 2011 to January 2012 under the guidance and supervision of Prof.Dr.S.Rukmangatharajan, MD., DM., FMMC., This dissertation is submitted to the Tamil Nadu Dr.M.G.R.Medical University towards the partial fulfillment of requirement for the award of D.M., Degree in Rheumatology.

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Place :

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ABBREVIATIONS

uSpA	Undifferentiated Spondyloarthropathy
SpA	Spondyloarthropathy
AS	Ankylosing Spondylitis
PsA	Psoriatic Arthritis
IBD	Inflammatory Bowel Disease
RA	Rheumatoid Arthritis
ER	Endoplasmic Reticulum
TAP	Transporter associated with Antigen Processing
PLC	Peptide Loading Complex
ERAP1	Endoplasmic Reticulum Aminopeptidase associated with antigen processing
ARTS1	Aminopeptidase Regulator of TNF receptor Shedding
ERAD	ER Associated Degradation
UPR	Unfolded Protein Response
ATF6	Activating Transcription Factor
IRE1	Inositol Requiring Enzyme
PERK	RNA activated Protein kinase(PKR) like ER Kinase
XBP	X box Binding Protein
BiP	Binding Immunoglobulin Protein
NFκB	Nuclear Factor kappa light chain enhancer of activated B cells

KIR	Killer cell Immunoglobulin like Receptors
ILT	Immunoglobulin Like Transcripts
MICA/MICB	MHC class I Chain related genes A and B
CARD	Caspase Recruitment Domain
LMP	Low Molecular weight Peptide
RFT	Renal Function Test
LFT	Liver Function Test
RF	Rheumatoid Factor
CRP	C Reactive Protein
ASO	Anti Streptolysin O
HLA	Human Leukocyte Antigen
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
HAQ	Health Assessment Questionnaire
TGFβ	Transforming Growth Factor β

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INTRODUCTION

Undifferentiated spondyloarthropathy is a syndrome with features consistent with the spondyloarthropathies but affected patients do not fulfill criteria for any specific spondyloarthropathy.[1]

Undifferentiated spondyloarthropathy may represent an early phase or incomplete form of ankylosing spondylitis or another spondyloarthropathy.

No large scale multinational studies have reported on the signs and symptoms of undifferentiated spondyloarthropathy. Because it is defined by the exclusion of traditionally well recognized arthritides, patients determined to have undifferentiated spondyloarthropathy probably exhibit a mixture of diverse signs and symptoms, one of which is either inflammatory low back ache or asymmetric oligoarthritis.[1]

No large scale longitudinal studies are available concerning the course and prognosis of undifferentiated spondyloarthropathy. Some studies show that after several years of follow up, some patients go into remission, some develop ankylosing spondylitis, and others continue to have undifferentiated spondyloarthropathy. A considerable number of patients were initially misdiagnosed with spondyloarthropathy, and their actual diagnoses, such as rheumatoid arthritis (RA) or gout, did not become clear until several years later. Clearly, a diagnostic method based on something other than expert opinion or classification criteria is needed. Most useful would be parameters that can predict whether a patient will progress rapidly into AS, because these patients might benefit from early aggressive therapy.[1]

AIMS AND OBJECTIVES

1) To study the clinical profile of undifferentiated spondyloarthropathy.

2) To assess the outcome of undifferentiated spondyloarthropathy after one year of follow up.

REVIEW OF LITERATURE

The spondyloarthropathies are a family of related disorders that includes ankylosing spondylitis, psoriatic arthritis, reactive arthritis, arthropathy of inflammatory bowel disease, juvenile ankylosing spondylitis and undifferentiated spondyloarthropathy.[5]

Undifferentiated spondyloarthropathy is a syndrome with features consistent with the spondyloarthropathies but affected patients do not fulfill criteria for any specific spondyloarthropathy.[1]

CLINICAL CHARACTERISTICS OF SPONDYLOARTHROPTHIES[5]

1) Typical pattern of peripheral arthritis- predominantly of lower limb, asymmetric.

2) Tendency towards radiographic sacroiliitis.

3) Absence of rheumatoid factor.

4) Absence of subcutaneous nodules and other extra articular features of rheumatoid arthritis.

5) Overlapping extra articular features characteristic of the group (eg:anterior uveitis)

6) Significant familial aggregation

7) Association with HLA -B27.

EPIDEMIOLOGY OF SPONDYLOARTHROPATHY

Indian data on the epidemiology of spondyloarthropathy are scarce. Prevalence data from the first Indian COPCORD (Community Oriented Program from Control of Rheumatic Diseases) survey showed the rural prevalence of back ache to be 17.3%. This included both inflammatory and mechanical back aches.[4] Of all the people with low back ache, about 1-2% are likely to have SpA. From this rural cohort, the SpA prevalence can be estimated at about 0.17-0.34%.

Data from a large clinic in North India (over 800 patients of rheumatic diseases on follow up) suggests that the ratio of rheumatoid arthritis (RA) to ankylosing spondylitis (AS) is about 3.2:1. Since the prevalence of RA in India is about 0.7%, that of AS is likely to be 0.2%.

The prevalence of AS in a population is directly related to the frequency of HLA B27 antigen in the community.[5] The frequency of HLA B27 in the North Indian population is 6%, similar to that in Caucasians. The prevalence of AS in Caucasians is 0-1%. Hence the prevalence in India is likely to be similar. Hence, by these three ways of reasoning, we could estimate the prevalence of SpA in India to be between 0.1 to 0.2%.

Prevalence data for uSpA are scarce, although this disorder appears to be at least as common as AS, if not more so. Its actual prevalence may be as high as 1-2% of the general population.

The male/female ratio is about 2/1 to 3/2 with an age of onset ranging from 16-70 years. Family history is positive in around 14% in undifferentiated spondyloarthropathy.[30]

PATHOGENESIS

The precise cause of spondyloarthropathy is unclear. There is a major genetic contribution. HLA B27 is directly involved in the pathogenesis of disease and additional non MHC genes contribute to the pathogenesis. Cartilage appears to be the primary target tissue for the abnormal immune response. Cytokine dysregulation with overexpression of TNFα and intestinal inflammation are prominent features of disease. Bone morphogenetic proteins (BMP) play a role in the pathogenesis of ankylosis.[5]

GENETIC FACTORS

The dominant role of genetic factors is highlighted by data demonstrating disease concordance in 75% of monozygotic twins compared with 13% of non identical twins, familial aggregation and association with HLA B27.[5]

HLA B27

HLA B27 contributes only 16% of the total genetic risk. Forty five subtypes have been assigned on the basis of nucleotide sequence homology that encodes more than 20 different products.[5] The most common subtype seen worldwide is B*2705, followed by B*2702. B*2706 is the most common subtype seen in Asians but it is neutral or weakly associated with disease. B*2709 is not associated with axial disease, although peripheral arthritis have been reported.[6]

The HLA B27 subtypes commonly seen in south india were HLA B*2704 and HLA B*2705. The prevalence of HLA B27 in India – in Tamilnadu 4.1% and in North India 6%.[7]

The main function of HLA B27 is to present peptides to CD8 T cells. Crystallographic analysis of B*2705 shows a peptide binding groove with pockets (A to F). The B pocket is conserved among B27 subtypes. It has a glutamine amino acid at position 45 that interacts with arginine at position 2 of B27 bound peptides. This pocket conveys specificity for the type of peptide bound to B27.[5]

ARTHRITOGENIC PEPTIDE HYPOTHESIS

It has been proposed that the antigen presenting properties of HLA B27 could be crucial in the pathogenesis of spondyloarthropathy.

Molecular Mimicry

Molecular mimicry is defined as the sharing of epitopes from disparate proteins. Although their origins may be as different as a microbe and a normal host protein, the linear amino acid sequences or the conformational fits of two such molecules may be homologous. An immune response, initiated by an invading microbe, i.e., bacterium, virus, or parasite, may then react not only with that microbe, but also with the homologous host protein. Conceptually, molecular mimicry can occur whenever the microbial and host determinants are sufficiently similar to induce a cross reacting immune response, yet different enough to break immunologic self tolerance.[10]

This hypothesis suggests that because of their unique aminoacid residues, some B27 subtypes bind specific arthritogenic bacterial peptides that are recognised by CD8 T cells. In response to these bacterial peptides, autoreactive T cell recognizing antigens with sufficient structural similarity between bacteria and self might become activated by self peptides such as those in joints and spine.[8] This process is supported by integrins, which are relevant for the homing of cross reactive CD8 T cells into the joint.

One major support for this hypothesis came from studies showing the differential association of natural HLA B27 subtypes to spondyloarthropathy. While B*2705, B*2702, B*2704 and B*2707 are strongly associated with disease, the subtypes B*2709 in Caucasians and B*2706 in Asians are not at all or only rarely present in spondyloarthropathy patients. These two subtypes differ from the disease associated ones only by one aminoacid substitution (B*2705 to B*2709) by exchange of an Asp^{116} to His^{116}, or two aminoacid substitutions (B*2704 to B*2706) by exchange of His^{114} to Asp^{114} and of Asp^{116} to Tyr^{116}, all of which are located in the peptide binding groove.[9] It has therefore been hypothesized that B*2706 and B*2709 subtypes do not present arthritogenic peptides in contrast with the disease associated ones.

This theory has been supported by animal studies also. B27 transgenic rats do not develop arthritis if maintained in a germ free environment. Exposure of these rats to bacteria, especially bacteroides species, triggers the onset of both intestinal and joint inflammation.

MOLECULAR MIMICRY BETWEEN HLA B27 AND BACTERIA

HLA B27 can also act as an autoantigen. Studies have shown there is molecular mimicry between the amino acid residues 72-77 of HLA B27 and 188-193 of Klebsiella pneumoniae nitrogenase reductase enzyme (QTDRED).[10] The cross reactivity between these antigens evokes immune response against the host. Experiments in Lewis rats have shown that the same B27 derived peptide is cross recognized with a homologous peptide derived from cytokeratin, a protein that is specifically expressed in synovial membranes, gut epithelium and eyes, and that immunization with either peptide induces arthritis and uveitis.

MISFOLDING OF PROTEINS

To transport the peptide to the cell surface, HLA class I heavy chains must fold properly, bind β2m and then load peptide prior to exiting the endoplasmic reticulum (ER) compartment. High stability of the trimolecular complex is essential for efficient transport through the golgi complex. The stability of HLA class I complexes is critically dependent on early events in the folding and assembly process, including the formation of two intrachain disulfide bonds.[11] The α3 domain folds very rapidly and is stabilized by an intradomain disulfide bond between Cys-203 and Cys-259. The α1 and α2 domains fold more slowly and this is not complete until peptide is stably bound. A second disulfide bond between the α1 and α2 domains (Cys-101 and Cys-164) maintains the integrity of the peptide binding groove[12] as the heavy chain/β_2m heterodimer interacts with tapasin, ERp57 and the transporter associated with antigen processing (TAP) to form the peptide loading

complex (PLC). HLA- B27 (the B*2705 subtype) is expressed relatively efficiently in tapasin-deficient cells[13] and is frequently referred to as a tapasin-independent allelle. The ability of HLA-B27 to be expressed at high levels on tapasin-deficient cells may reflect its tendency to fold slowly and be retained in the ER in a peptide receptive state without tapasin-PLC interaction.[14] This could favor the binding and optimization of available peptides without tapasin mediated retention.

ERp57 binds to tapasin via a disulfide bond and plays an important role in disulfide bond isomerization in the heavy chain during class I assembly. Recent evidence indicates that formation of the ERp57-tapasin conjugate prevents ERp57- mediated reduction of the α1α2 interdomain disulfide in the class I heavy chain, thus maintaining the peptide binding groove in a receptive state. When tapasin is missing or mutated at Cys-95 and thus unable to form a complex with ERp57, the class I heavy chain α1α2 disulfide is reduced until suitable peptide can bind. Free ERp57 (or ERp57-calreticulin complexes) appears to catalyze this reduction in the absence of tapasin leading to the concept that tapasin performs its function by sequestering ERp57.

The final stages of peptide binding to HLA class I molecules includes trimming by the ER aminopeptidase associated with antigen processing (ERAP1).[15] In addition to peptide trimming for presentation by class I molecules, ERAP1 appears to have another role in the immune system. It was discovered independently as Aminopeptidase Regulator of TNF Receptor

Shedding (ARTS-1), but also regulates shedding of IL-6 and IL-1 decoy receptors.

There are molecular chaperone systems that assist and monitor the folding process to ensure high fidelity production of proteins that can function properly. When protein folding does not occur properly, due to mutations or polymorphims that alter the aminoacid sequence, or abnormalities in components of the chaperone systems, misfolding can result. Many misfolded and even incompletely folded ER proteins can be eliminated efficiently by ER-associated degradation (ERAD) if they have remained in the ER for a sufficient time. The cellular response to ER protein misfolding referred to as the UPR (unfolded protein response), is part of a more global homeostatic response to ER stress.

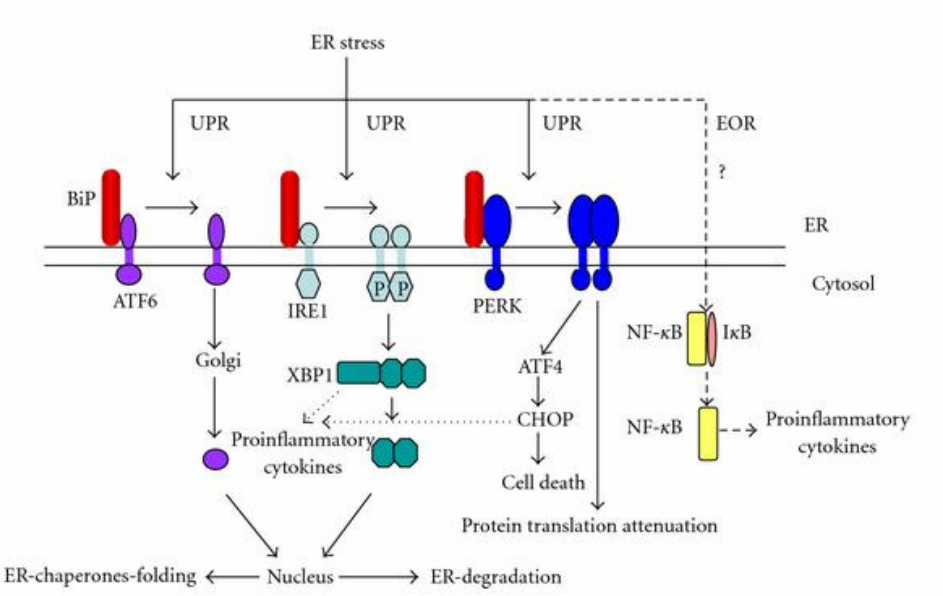
THE UNFOLDED PROTEIN RESPONSE

One of the consequences of protein misfolding in the ER can be activation of the UPR. There are three main effector molecules of the UPR, the ATF6 transcription factor and the two kinases IRE1 and PERK. These effector molecules reside within the ER and are maintained in an inactive state by the ER resident chaperone Immounoglobulin Binding Protein (BiP).

During ER stress, BiP is sequestered away from these effector molecules, leading to their activation. Dissociation from BiP unmasks targeting signals, which translocate ATF6 to the golgi apparatus. Within the golgi apparatus, proteolytic processing of the ATF6 cytosolic domain by two resident proteases. The ATF6 cytosolic domain is then translocated to the nucleus and acts as a potent transcription factor upregulating chaperones

participating in protein folding. Prolonged ER stress can induce the oligomerisation and autophosphorylation of the ER resident IRE1 and PERK kinases. Phosphorylated IRE1 can splice the cytosolically located XBP1 mRNA. XBP1 can activate chaperones to enhance cellular folding capacity and/or proteins involved in the degradation of misfolding substrates. Activated PERK can phosphorylate elongation factor 2α (eF2α), which inhibits protein synthesis, thus reducing the protein load within the ER. Furthermore PERK can activate a series of transcription factors which can lead to the induction of apoptosis, thus leading to the removal of terminally distressed cells. The ER overload response remains poorly defined, but it is thought that accumulation of misfolded proteins within the ER leads to the activation of the transcription factor NFκB. As NFκB can target proinflammatory cytokine genes, activation of this transcription factor could be a key link between HLA-B27 misfolding and the production of proinflammatory cytokines IL-1 and TNFα.[16]

Furthermore, proinflammatory cytokines, notably TNFα, can induce ER stress. This raises the possibility that, if HLA-B27 misfolding does induce ER stress and lead to proinflammatory cytokine production, this could develop into a positive feedback loop which exacerbates and perpetuates the release of TNFα and other pro-inflammatory mediators. Thus there does indeed appear to be a link between ER stress and a proinflammatory cytokine environment, which is a characteristic feature of SpA patients.



HEAVY CHAIN HOMODIMER FORMATION

An unusual characteristic feature of HLA B27 is its ability to form heavy chain homodimers. This property is dependent on the rare cysteine residue at position 67 which can form a disulfide bridge but cysteine residues at other positions can also form homo dimers (eg: position 164). B27 is not the only HLA class I molecule that can form dimers. HLA A2 can also form homodimers. The property of B27 to form dimers may be related to its misfolding.[19]

KILLER CELL IMMUNOGLOBULIN LIKE RECEPTORS

HLA B27 homodimers were recognized by receptors belonging to a family called killer cell immunoglobulin like receptor (KIR) family. Killer cell immunoglobulin like receptors (KIRs) are expressed on natural killer (NK) cells and some T cells, including activated $CD8^+$ T cells that interact with class I HLA molecules (including HLA-B27). There are many receptors, of which KIR3DL1 and KIR3DS1 are important in the pathogenesis of SpA.

HLA B27 can be recognized by KIR3DL1 conferring a strong inhibition and preventing lysis of the cell. Recognition of B27 by KIR3DL1 can be blocked (some viral peptides may cause the blockage of the inhibitory receptor 3DL1 or KIR3DL1 polymorphism can serve to alter the inhibitory response).[17] So, a microbial infection can cause activation of activating NK receptors (KIR3DS1) and the subsequent progression to AS.[18]

Heavy chain homodimers can also bind with immunoglobulin like transcripts (ILT) or leukocyte Ig like receptor family. Homodimer binding with KIR and ILT has been shown to stimulate the release of TNFα.

NON B27 HLA GENES

HLA B60 carries an increased risk for spondyloarthropathy. Associations of B27 negative AS have also been reported with HLA alleles in the B27 cross reactive group (B7, B22, B40, B41, B42). An increased risk has been associated with HLA B39.

Polymorphism in TNFα has been associated with spondyloarthropathy. A significant decrease in the A allele at position 308 has been found in spondyloarthropathy.

Polymorphisms in MHC class I chain related genes A and B (MICA and MICB) also contributes to spondyloarthropathy.[19]

NON HLA GENES

Case control studies in Caucasians and Taiwanese populations show an association with cytochrome P-450 CYP 2D6 gene which is involved in the metabolism of drugs. An association has also been seen with CARD15 and

intestinal inflammation. CARD15 binds to bacterial cell wall components and is a regulator of proinflammatory NFκB.[5]

IL-I gene cluster is an important loci associated with susceptibility to spondyloarthropathy.

ARTS1 gene is also associated with spondyloarthropathy. This gene encodes the endoplasmic reticulum aminopeptidase, which cleaves cytokine receptors for IL-1 and TNFα from the cell surface and is important in antigen presentation by class I MHC molecules.

The IL-23R gene which encodes the receptor for IL-23 is associated with spondyloarthropathy. IL-23 promotes survival of Th17 cells which produces IL-17, IL-6 and TNFα, and recruits inflammatory cells.

Genes possibly associated with spondyloarthropathy includes ANKH gene (involved in transport of inorganic pyrophosphate from intracellular to extracellular compartments) and HLA DRB1.[19]

ROLE OF BACTERIA

B27 transgenic rats do not develop arthritis if maintained in a germ free environment. Exposure of these rats to bacteria, especially bacteroides species, triggers the onset of both intestinal and joint inflammation. In humans, evidence of intestinal inflammation is present in upto 60% of spondyloarthropathy patients. Elevated immunoglobulin IgA antibodies to several bacteria have been observed, such as Klebsiella pneumoniae and E.coli, but bacterial products have not been detected in sacro iliac joint biopsies. Antigen presenting cells in intestinal mucosa and synovium that

express the CD163 scavenger receptor possess the capacity to secrete TNFα and IL-1 in response to bacterial lipopolysaccharide.[5]

ROLE OF TNFA

1) Stimulation of endothelial cells to express adhesion molecules

2) Recruitment of leukocytes into the inflamed synovium

3) Induction of inflammatory cytokine production like IL-1,IL-6

4) Stimulation of synovial cells to release collagenases

5) Induction of bone and cartilage resorption

6) Stimulation of fibroblast proliferation.

CD4+ T CELLS IN SPONDYLOARTHROPATHY

On the basis of evidence from the HLA-B27 transgenic animal models and the identification of an HLA-B27 homodimer structure which might mimic the structure of a MHC class II molecule, it has been hypothesized that CD4+ T cells, which conventionally recognize MHC class II molecules, can recognize the MHC class I molecule HLA-B27, breaking the conventional rules of MHC restriction. There are large numbers of CD4+ T cells in diseased joints which implies that CD4+ T cells plays a role in the pathogenesis of spondyloarthropathy.

Recognition of empty HLA-B27 heterodimers

One type of HLA-B27 reactive CD4+ T cell isolated, responded only to HLA-B27 expressed on the processing defective cell lines and did not respond to HLA-B27 expressed on peripheral blood mononuclear cells (PBMC) and

Epstein Barr virus(EBV) transformed cell lines. Therefore it was unlikely that a conventional form of HLA-B27 was recognized. Further studies implied that 'empty' or 'peptide-receptive' HLA-B27 heterodimers were recognized by these CD4+ T cells (i.e.,heterodimers devoid of peptide). MHC class I antigen processing pathway defects occur in humans by the following ways.[22]

1) Due to genetic defects in essential components of the MHC class I processing pathway – mutations in the β2m gene and defects in the expression of TAP and LMP genes.

2) During infection with intracellular pathogens – alterations to the MHC class I processing pathway are most commonly observed during viral infection, eg: Cytomegalovirus and Herpes simplex infection.

3) As a result of the action of cytokines – the ability of human IL-10 to efficiently down-regulate the expression of the LMP2 and TAP1 genes, which results in inefficient transport of peptides into the ER, indicates that constitutive or induced IL-10 production or altered cytokine patterns could lead to deficiencies in the MHC class I processing pathway.[22]

Recognition of an abnormally folded HLA-B27 complex

A second type of HLA-B27 reactive CD4+ T cells recognize the epitope expressed on an abnormally folded form of HLA-B27, possibly a homodimeric structure of HLA-B27. Whether this structure also presents an antigenic peptide to the CD4+ T cells is unknown. The fact that responses are considerably enhanced by the transfection of TAP suggests that there is a

requirement for a TAP transported antigenic peptide. TAP dependent peptides stabilize this form of HLA-B27.

Initial activation of these CD4+ T cells would probably require traffic of antigen presenting cells bearing altered forms of HLA-B27 (eg:infected dendritic cells) to regional lymph nodes, but subsequent recruitment of primed cells to the joint or to entheses would result in their activation if altered forms of HLA-B27 were present locally.

Activation of these CD4+ T cells would result in the induction of an inflammatory response, with recruitment of inflammatory cells, such as macrophages and other phagocytic cells, to entheses or synovium, where they could be activated and release inflammatory cytokines. The release of IL-8, TNFα and IL-12 at this site would activate the vascular endothelium, increase vascular permeability and activate lymphocytes and natural killer cells. Alternatively, if these CD4+ T cells provide help for B cells, this could result in the high levels of IgA seen in SpA, particularly if the T cells also secrete TGFβ. Subsequent complement activation would result in the lysis of cells by the membrane attack complex, cytokine and prostaglandin release and the recruitment of inflammatory cells, and likewise tissue injury from products of activated leukocytes. The persistence of antigen, in this case unusual forms of HLA-B27, would result in continued inflammation leading to tissue destruction.[22]

PATHOLOGY

SACROILIAC JOINT

This is an anatomically complex joint. The anteroinferior portion (lower two third) is a synovial joint. The posterosuperior portion is ligamentous. The cartilage overlying the sacrum is thick and resembles hyaline cartilage. It is supported by relatively thin bony endplate. In contrast, the iliac cartilage resembles fibrocartilage with more fibres and less proteoglycan. It is supported by a thicker subchondral bony endplate.

In early stages of sacroiliitis, there is cellular infiltration with lymphocytes, macrophages and plasma cells in the synovium and subchondral marrow. Later features include the development of pannus extending from both synovium and subchondral bone marrow, with erosions of articular cartilage.

Reparative changes include cartilage metaplasia at sites of active inflammation, followed by its calcification and ossification leading to bony ankylosis. Immunohistological studies show the presence of T lymphocytes and macrophages expressing TNFα. Transforming growth factor is evident at sites of new bone formation.[5]

SPINAL LESIONS

In most of the patients, the disease progress to involve the spine with a predilection for apophyseal joints, intervertebral discs, costovertebral and costotransverse joints and extra-articular spinal ligaments.[19]

APOPHYSEAL JOINTS

Early involvement of the apophyseal joints was located at the bony attachment of the joint capsule and was accompanied by increased fibroblasts, small vessels, lymphocytes, plasma cells and macrophages which leads to destruction of capsular insertion and adjacent bone and forms a pannus that erodes the margins of articular cartilage.

Advanced changes include calcification of articular cartilage, chondroid metaplasia and ossification of sub-synovium and fibrous capsule usually starting at its insertion. Ultimately joint undergoes central cartilage fusion and peripheral ossification leading to marginal ankylosis forming a complete tube before the main part of the articular cartilage is also destroyed.

Once the joint has become immobile, the superficial layer of articular cartilage becomes necrotic and replaced by ossifying connective tissue leading to a bony plate between the remnants of cartilage plates.

Progression of disease is typically ascending so that higher levels of spine are progressively affected although it is not unusual to see advanced disease in the cervical apophyseal joints with minimal changes at lower levels. Apophyseal joint inflammation and ankylosis may also precede ankylosis of adjacent intervertebral disc space. This indicates that the immobilization caused by apophyseal joint ankylosis may be a factor in the development of vertebral ankylosis.

Immunohistological analysis of apophyseal joints has shown subchondral infiltrates of CD4 and CD8 T cells and hypervascularisation and foci of CD68 osteoclastic cells.[20]

INTERVERTEBRAL DISCS

The most common initial feature is the appearance of granulation tissue either along the whole outer annulus fibrosus or at its attachment to the bone anywhere on the circumference. There are infiltrates of lymphocytes, plasma cells and macrophages. Initially there is destruction of the anterior side of the normally bulging vertebral rim which is followed by bony proliferation in the adjacent trabecular bone and in the area of the destroyed annular fibres. The bony proliferation then grows in the direction of the annulus fibrosus, perpendicular to the vertebral axis.[19]

ATLANTOAXIAL AREA

The atlantoaxial region of the upper cervical spine which is rich in fibrocartilage, especially where the transverse ligament attaches to the arch of atlas has more predilection. Erosion of the insertion of the transverse ligament into the arch of atlas, in combination with destruction of the lateral atlantoaxial joint ultimately lead to atlantoaxial dislocation and cord compression. Late findings include ankylosis of the joint and osteosclerosis of the odontoid process of the axis.[19]

COSTOVERTEBRAL AND COSTOTRANSVERSE JOINTS

Inflammation in these joints typically manifest as subchondral bone marrow edema. Histopathological examination shows synovitis and granulation tissue eroding the articular cartilage as pannus. Late features

include chondroid metaplasia, syndesmosis and marginal ankylosis leading to restriction of chest movement and decreased vital capacity of lungs.[19]

EXTRA-ARTICULAR SPINAL LIGAMENTS

Marrow inflammation, bone erosion followed by ankylosis typically involve the intraspinal, supraspinal ligaments and ligamentum flavum. The anterior and posterior longitudinal ligaments along the vertebral bodies are usually not affected by ossification.[19]

ENTHESIS

ANATOMY AND PATHOLOGY

The enthesis is defined as the site of insertion of a tendon, ligament, joint capsule or fascia into the periosteum of bone. There are two major types:

1) Fibrous – pure dense fibrous connective tissue that links the tendon or ligament to bone. In long bones, fibrous entheses are located at a considerable distance from a joint and are thus typical of tendons / ligaments attached to diaphyses. Eg : deltoid and pronator teres.

2) Fibrocartilaginous – transitional zone of fibrocartilage at the bony interface.[21]

These are characteristic of tendons and ligaments attached to epiphyses and apophyses, where the direction of force transmitted by the tendon / ligament changes throughout the range of joint movement. Eg : Achilles tendon, tendon of supraspinatus.

Fibrocartilage is a dynamic tissue that develops at sites where entheses are subjected to shear and compressive forces. It has the ability to promote bone formation.[21]

Entheses are well supplied with pain and proprioceptive receptors. Recent animal studies have shown that enthesis itself is aneural and that nerve fibres are restricted to neighbouring tissues. Thus in its lack of nerve fibers, enthesis fibrocartilage parallels the articular cartilage of a synovial joint. The fibrocartilage is also avascular and the blood supply is derived from vessels in the peritenon, perichondrium, periosteum and adjacent bone marrow.

Disease in spondyloarthtropathy is virtually restricted to fibrocartilaginous entheses. Four zones of tissues are recognised at attachment sites. They are,

1) Dense fibrous connective tissue – parallel bundles of collagen bundles separated by longitudinal rows of fibrocartilage.

2) Uncalcified fibrocartilage – fibrocartilage cells commonly arranged in longitudinal rows, replace the fibroblasts. These are associated with matrix type II collagen fibers and proteoglycan.

3) Calcified fibrocartilage – less cellular than its uncalcified counterpart and having an extracellular matrix that is heavily calcified. A straight interface called the 'tidemark' separates calcified from uncalcified fibrocartilage and is the mechanical boundary between hard and soft tissues.[21]

4) Bone – a bony cortex at a fibrocartilaginous enthesis barely exists, for even in a large tendon like the Achilles, the subchondral bone plate is generally little thicker than one or two trabeculae. Indeed, the cortex can be totally absent. Therefore bone at the site of enthesis is closely integrated with adjacent trabecular bone. There are complex interdigitations of bone and calcified fibrocartilage that knit them into each other, promoting the basic function of tendon/ligament anchorage. There are no Sharpey's fibers where fibrocartilage is present at entheses, as the subchondral bone plate is too thin. Sharpey's fibers are a particular feature of fibrous entheses.[21]

HISTOPATHOLOGY

Chronic enthesitis is characterized by bony erosions and destruction, with inflammatory infiltrates evident in the bone adjacent to the enthesis. Inflammatory cells including macrophages and T lymphocytes and edema in the bone marrow close to fibrocartilage are observed. In later disease, capsular ossification, myxoid bone marrow changes, chondroid metaplasia, ossification and formation of synchondroses are reported. The only direct evidence for TNF involvement at human entheses comes from studies in which TNF blockade leads to regression of enthesitis/osteitis as determined by MRI.

ENTHESITIS – BASED MODEL

Small particles (0.002-1.1 µm in diameter)such as bacteria may localize to transitional zones such as entheses, where richly and poorly

vascularised areas are juxtraposed. Bacteria or their macromolecules contribute to inflammation by unknown mechanisms.

Biomechanical stress occurs at entheses in addition to other sites such as aorta, lung apex, uvea in spondyloarthropathy. This suggests that stress in the presence of microtrauma and subsequent healing along with deposition of bacterial products, may convert a physiological healing response into an inflammatory response. Relevant features include the special vascularity of entheses, with subsequent activation of Toll-like receptors by CpG motifs, lipopolysaccharide or bacterial heat shock proteins. These may either directly or indirectly induce NFκB activation that triggers an inflammatory reaction with dendritic cell activation and T cell co-stimulation leading to HLA-B27 related immune responses. Bacterial structural proteins and DNA alone, without viable organisms can initiate inflammatory response at entheseal sites.[21]

CLINICAL FEATURES

LOW BACK PAIN

Inflammatory type of low back ache is a common presentation seen in 90% of undifferentiated spondyloarthropathy patients. The pain is initially felt deep in the gluteal region, dull in character, difficult to localize and is insidious in onset. The buttock pain typically alternates from side to side. Buttock pain is seen in 80% of undifferentiated spondyloarthropathy patients.

Although the pain is often unilateral or intermittent at first, within a few months, it usually becomes persistent and bilateral. The pain is associated with a feeling of low back stiffness that is worse in the morning

and may awaken the patient from sleep, particularly in the second half of night. Morning stiffness may last upto 3 hours. Both the stiffness and low back ache tend to be eased by a hot shower bath, an exercise program or physical activity; they do not improve with rest.[23]

BERLIN CRITERIA FOR INFLAMMATORY BACK ACHE IN PATIENTS WITH CHRONIC BACK ACHE (>3 MONTHS)[36]

1) Morning stiffness > 30 minutes

2) Improvement with exercise but not with rest

3) Awakening at second half of the night because of back pain

4) Alternating buttock pain

The criteria are fulfilled if atleast two out of four parameters are present.

ENTHESITIS

Extra articular pain at certain sites is a common complaint in some patients. These lesions are due to enthesitis. Common sites include spinous processes, iliac crests, greater trochanters, ischial tuberosities, tibial tubercles, costosternal junctions and heels (Achilles enthesitis or plantar fasciitis). Enthesitis is seen in 85% of patients with undifferentiated spondyloarthropathy

CHEST PAIN

With subsequent involvement of the thoracic spine (including costovertebral and costotransverse joints) and the occurrence of enthesopathy

at the costosternal and manubriosternal joints, patient may experience chest pain accentuated by coughing or sneezing, which is sometimes characterized as pleuritic. Mild to moderate reduction of chest expansion is often detectable. Chest pain occurs relatively often in HLA B27 positive relatives, even in the absence of radiographic evidence of sacroiliitis.[24]

ARTHRITIS

Hips and shoulders (root joints) are the most frequently involved extra axial joints. Peripheral arthritis is seen in 35%. It affects predominantly the lower limbs as asymmetrical oligoarthritis. Knee joints are commonly involved.

DACTYLITIS

Dactylitis is swelling of an entire finger or toe due to synovitis and tenosynovitis. It is seen in 17% of undifferentiated spondyloarthropathy.

EXTRA ARTICULAR MANIFESTATIONS

Extra articular manifestations are uncommon occurring in less than 10% of patients and include acute anterior uveitis, cardiac problems, oral ulcers, rash, non specific colitis and osteoporosis. Due to restricted chest wall movement, vital capacity may be moderately reduced, whereas residual volume is usually increased.

UVEITIS

Acute anterior uveitis is the most common extra articular manifestation. It is seen in 1-2% of undifferentiated spondyloarthropathy.

There is no clear relationship between activity of the articular disease and uveitis.[5]

The onset of uveitis is usually acute and typically unilateral but the attacks may alternate. The eye is red and painful, with visual impairment. Photophobia and increased lacrimation may be present. If the eye remains untreated or if treatment is delayed, posterior synechiae and glaucoma may develop. Most attacks subside in 4 -8 weeks without sequelae if early treatment is provided. Acute anterior uveitis is more common in B27 positive than B27 negative patients.[25]

CARDIAC MANIFESTATIONS

Cardiac involvement may be clinically silent or may cause considerable problems. Manifestations of cardiac involvement include ascending aortitis, aortic valve incompetence, conduction abnormalities, cardiomegaly and pericarditis. In rare situations, aortitis may precede other features of SpA. Aortic incompetence was noted in 3.5% of patients who had the disease for 15 years and in 10% after 30 years.[26] Inflammation and dilation of the aorta are the main causes of aortic valve incompetence.

Cardiac conduction disturbances are seen with increasing frequency with the passage of time, occurring in 2.7% of those with disease of 15 years duration and in 8.5% after 30 years. Both aortic incompetence and cardiac conduction defects occur twice as often in patients with peripheral joint involvement.

PHYSICAL FINDINGS

LUMBAR SPINE

On examination of the spine there may be some limitation of movement of the lumbar spine as elicited by forward flexion, hyperextension or lateral flexion. Early loss of the normal lumbar lordosis is often the first sign and is easily assessed on inspection.

SCHOBER'S TEST

The Schober test is used to detect limitation of forward flexion of the lumbar spine although it is typically normal in early disease. As the patient stands erect, one mark is placed on the skin overlying the fifth lumbar spinous process (usually at the level of the posterior superior iliac spine or the dimple of venus) and another mark is placed 10 cm above in the midline. The patient is then asked to bend forward maximally without bending the knees. If the distance between the both marks does not reach 15 cm, this indicates reduced lumbar spine mobility.[5]

In modified Schober's test, one mark is placed at the level of fifth lumbar spinous process. Second mark is placed 10 cm above in the midline. Third mark is placed 5 cm below in the midline. The patient is then asked to bend and if the distance between the second and third marks doesn't reach 20 cm, it indicates reduced lumbar spine mobility.

Lateral lumbar flexion- The patient bends laterally to push the middle finger down without flexing forward or bending the knees. The difference between the start and end point is recorded and the mean calculated; normal > 10 cm.

CERVICAL SPINE

1) Cervical rotation: the mean of the right and left cervical rotation is recorded. Normal >70 degrees[27]

2) Occiput to wall distance: patient stands, heels and buttocks against the wall, the head is placed back as far as possible, keeping the chin horizantal. Normal = 0 cm.[27]

3) Tragus to wall distance: patient stands, heels and buttocks against the wall, the head is placed back as far as possible, keeping the chin horizantal. Normal <15 cm.[27]

CHEST EXPANSION

Chest expansion should be measured on maximal inspiration after forced maximal expiration at the level of the 4th intercostal space in males and just below the breast at the xiphisternal level in females. Normal values are age and sex dependent. Reduction below 5 cm in young persons is abnormal.[5]

SACROILIITIS

1) Direct pressure over the sacroiliac joints may elicit pain.

2) Pelvic compression test: With the patient in side lying position, downward pressure is applied to the uppermost iliac crest directed towards the opposite iliac crest. It is intended to stretch the posterior sacro iliac ligament.

3) Pelvic distraction test: With the patient lying supine, a posterior and lateral force is applied to both anterior superior iliac spine. It is intended to stretch the anterior sacroiliac ligament.

4) Patrick test (FABER): This test stretches hip and sacroiliac joint. The patient is asked to do flexion, abduction and external rotation of the hip. A positive test produces back / buttock pain whereas groin pain is indicative of hip pathology.[28]

5) Gaenslen's test: The patient should be placed at the edge of the table. With the patient lying supine, the hip is maximally flexed on one side and on the opposite side, the leg is allowed to fall over the side of the side of the examination table. This stretches the sacroiliac joint and produces pain.

LABORATORY TESTS

Generally routine blood tests are not helpful. A normal ESR or normal CRP does not exclude active disease.[5] An elevated ESR or CRP is reported in upto 36% of patients, but it may not correlate with clinical disease activity. Renal and liver function tests should be done before starting the DMARDS therapy.

HLA B27

Typing for human leukocyte antigen (HLA-B27) has been suggested as a clinically valuable diagnostic test for ankylosing spondylitis, Reiter's syndrome, arthropathy of inflammatory bowel disease and undifferentiated spondyloarthropathy. Diagnosis can be made in most patients with diseases on

the basis of the history, physical examination and radiologic findings. The B27 test cannot be used to screen an asymptomatic population to detect these diseases and should not be thought of a routine diagnostic test.

Over 90% of all patients with ankylosing spondylitis carry the HLA-B27 gene, which however is only present in 8% of the healthy population. HLA B27 positivity varies in different studies from 25- 80%.[29]

It can be helpful in the diagnosis of suspected cases of spondyloarthropathy.

1) Patients with asymmetric oligoarthritis in lower limbs and enthesitis

2) Patients with inflammatory back ache but no sacroiliitis on imaging.

3) Anterior uveitis.

HLA-B27 is not a definitive test that can be used to diagnose or rule out a disorder.

HLA-B27 is detected by microlymphocytotoxicity, flow cytometry and polymerase chain reaction.

IMAGING STUDIES

CONVENTIONAL RADIOGRAPHY

X rays are not suitable for early diagnosis of spondyloarthropathy. Radiologically sacroiliitis can be present, but it should be either unilateral/bilateral grade I or unilateral grade II.

GRADING OF RADIOGRAPHIC SACROILIITIS

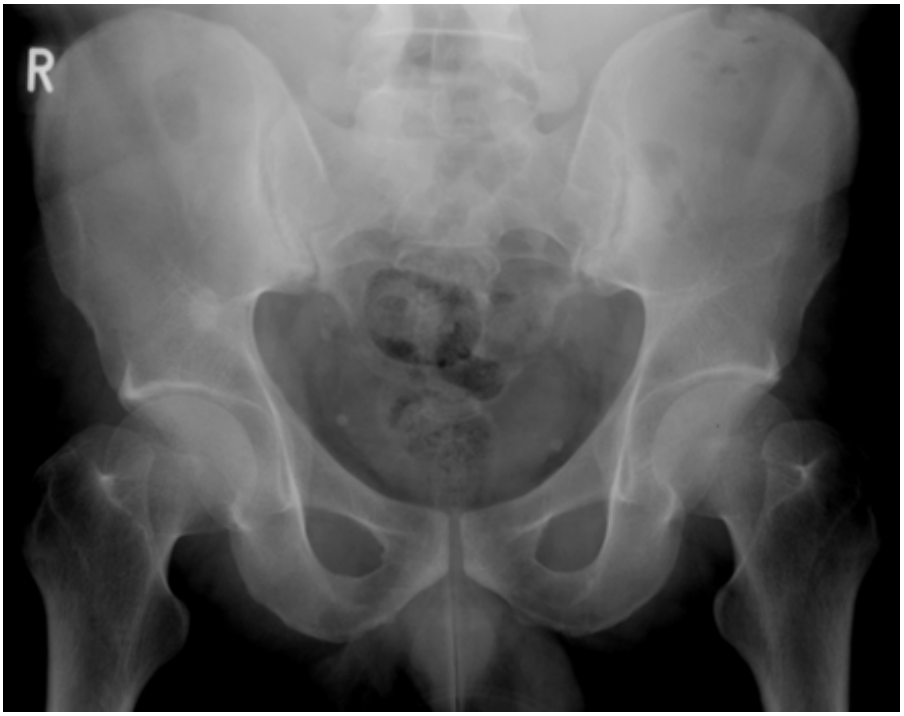
Grade 0 : normal

Grade 1 : suspicious

Grade 2 : minimal sacroiliitis- small localized areas with erosions or sclerosis, without alterations in joint width.

Grade 3 : moderate sacroiliitis – with one or more of : erosions, sclerosis, pseudowidening, narrowing or fibrous ankylosis

Grade 4 : bony ankylosis.



X-ray pelvis showing bilateral grade II sacroiliitis.

X-RAY SPINE

Spinal lesions without sacroiliitis are never observed, although zygoapophyseal joint involvement at a certain level and squaring can be present and be the first manifestation of spinal involvement.[30]

MRI

MRI studies of the sacroiliac joints and spine in spondyloarthropathy patients detects the early stages of sacroiliitis and have been used as an objective outcome measure for clinical trials.

Active inflammatory changes are seen best by fat saturated T2 weighted turbo spin-echo sequence or a short tau inversion recovery (STIR) sequence which can detect even minor fluid collections such as bone marrow edema. Alternatively administration of a paramagnetic contrast medium (gadolinium) detects increased perfusion (osteitis) in a T1 weighted sequence with fat saturation. Active inflammatory lesions appear as hyperintense signals. Apart from bone marrow edema, STIR/ post-gadolinium T1 sequence detects capsulitis, synovitis and enthesitis.

Chronic inflammatory lesions are best seen with T1 weighted sequence. It helps to detect sclerosis, erosions, fat deposition and bony bridges/ankylosis.

Spinal inflammation can also be assessed by MRI. Romanus lesions appear as hypointense signal on T1 weighted image, hyperintense on post-gadolinium T1 and STIR sequences. They also helps to detect spondylodiscitis. Contrast enhancement was absent in cases of syndesmophyte

formation. Syndesmophytes are best seen with T1 weighted images. Posterior elements such as facet joints, pedicles and transverse processes can show inflammatory lesions.

MRI is very useful to assess enthesitis problems such as Achilles enthesitis and plantar fasciitis.[31]

CT

CT scan is usually considered superior to MRI for diagnosing joint erosions, subchondral sclerosis and bony ankylosis. It is also useful to diagnose spinal fractures.

ULTRASOUND

Ultrasound is useful for imaging the peripheral joints. It can detect synovial effusions, synovial thickening, tenosynovitis. Ultrasound is relatively inexpensive and does not convey radiation exposure that is inherent in conventional radiography.

Ultrasound helps to diagnose enthesitis. The ultrasound appearance of enthesitis is that of hypoechoic thickening and edema, with erosion, new bone formation or changes in entheseal vascularity on power doppler ultrasonography.[21]

The abnormal flow signs at the sacroiliac joints can be detected by power doppler ultrasonography. Low resistance index values and vascularisation of the sacroiliac joints provide evidence for active sacroiliitis. Doppler USG is more sensitive in detecting sacroiliitis than in detecting enthesitis.[31]

BONE SCINTIGRAPHY

Bone scintigraphy is a useful adjunct for evaluating sacroiliac joint disease. It confirms the presence of hyperemia and inflammation that may not be seen radiographically.[31]

OUTCOME OF UNDIFFERENTIATED SPONDYLOARTHROPATHY

In the adult population a significant number of patients with undifferentiated spondyloarthropathy can progress to a definite spondyloarthropathy (ankylosing spondylitis, psoriatic arthritis, arthropathy of IBD) after a variable length of follow up. Sany et al. found a definite SpA in 30% of 23 HLA B27 positive uSpA patients after 28 months of follow up. Schattenkirchner and Kruger et al. with their study of 119 patients with HLA B27 positive oligoarthritis during a follow up of 2-6 years, observed that 25% progressed to a definite SpA, 26% had recurrent oligoarthritis and 34% were asymptomatic. After a ten year follow up study, Mau et al. observed a progression to ankylosing spondylitis in 59% of 54 patients (from the original 88 patients) who completed the study. In an Indian study by Kumar et al. analyzing the 11 year follow up of 22 patients with uSpA, 15 (68%) progressed to ankylosing spondylitis, one developed psoriatic arthritis, two went into natural remission and four continued with uSpA. Sampaio Barros et al. found that after a follow up of ten years with 111 patients, 27 (24.3%) patients progressed to AS, 3 (2.7%) patients to PsA while 25 (22.5%) patients went into remission.[32,33,34]

PROGNOSIS

The following factors are associated with a poorer prognosis in spondyloarthropathy.[35]

1) Older age at onset

2) Male sex

3) Smoking

4) Longer disease duration and greater severity

5) Hip involvement

6) Extra-axial involvement (number of peripheral joints affected, extent of enthesitis)

7) Eye involvement

8) Raised acute phase reactants (ESR, CRP)

9) Poor response to NSAIDS

10) Presence of radiological changes at baseline

11) Presence of HLA-B*4100, DRB1*0804, DQA1*0401, DQB1*0603, DRB1*0801 and DPB1*0202 alleles

SpA in women may not be as severe as it is in men and may present with isolated neck pain in the absence of typical back pain. Women tend to have less severe involvement of the spine with peripheral joint involvement. SpA did not adversely affect the ability to conceive, pregnancy outcome or neonatal health.

MATERIALS AND METHODS

Place of study	:	Department of Rheumatology, Rajiv Gandhi Government General Hospital & Madras Medical College, Chennai-3
Type of study	:	Prospective study.
Duration of the study	:	1 year (February 2011 to January 2012)
Ethical Committee	:	Present dissertation was approved by the Institutional Ethics Committee.
Consent	:	Informed written consent was obtained from all the patients.

MATERIALS

40 consecutive undifferentiated spondyloarthropathy patients attending the Department of Rheumatology outpatient clinics and patients in Rheumatology wards were included in this study.

INCLUSION CRITERIA

Patients who satisfy European Spondyloarthropathy Study Group Criteria.

EUROPEAN SPONDYLOARTHROPATHY STUDY GROUP (ESSG) CRITERIA [3]

Inflammatory spinal pain OR Synovitis (asymmetric, predominantly in lower limbs)

and

Any one of the following

Positive family history

Psoriasis

Inflammatory bowel disease

Alternate buttock pain

Enthesopathy

Non gonococcalacute urethritis, cervicitis or acute diarrhoea within one month before arthritis

Sacroiliitis

EXCLUSION CRITERIA

Ankylosing Spondylitis (definite)

Psoriatic arthritis

Reactive Arthiritis

Arthropathy of Inflammatory Bowel Disease

Juvenile Ankylosing Spondylitis

Rheumatoid Arthritis

METHODS

Each patient underwent detailed history regarding the age of onset of the disease, duration, low back ache, joint pain and swelling, entheseal pain and red eyes. Then patients were examined for involvement of sacroiliac joints, peripheral arthritis, dactylitis, enthesitis and uveitis. BASDAI, BASFI, BASMI and HAQ were done at baseline and after one year. Laboratory parameters included hemogram, RFT, LFT, RF, CRP, ASO and HLA B27. X ray pelvis was taken at the study entry and after one year.

ANALYSIS

To analyse the clinical profile of undifferentiated spondyloarthropathy - age of onset, gender predisposition, disease duration,presence or absence of sacroiliitis, pattern of peripheral arthritis, dactylitis, enthesitis, uveitis, elevation of acute phase reactants ESR/ CRP, HLA B27 positivity, BASDAI, BASFI, BASMI, HAQ.

To study the outcome of undifferentiated spondyloarthropathy after one year of follow up – whether they develop into ankylosing spondylitis / psoriatic arthritis / arthropathy of inflammatory bowel disease or they continue to be undifferentiated spondyloarthropathy.

STATISTICAL ANALYSIS

Mean and standard deviation were computed for continuous data and proportion was calculated for discrete data. To compare the mean values between the two groups independent t-test was used. The chi-square test was employed to compare the proportion between the two groups. Analysis was

two tailed and p-value < 0.05 was considered for statistically significant. Statistical analysis was performed by using SPSS version 16 package.

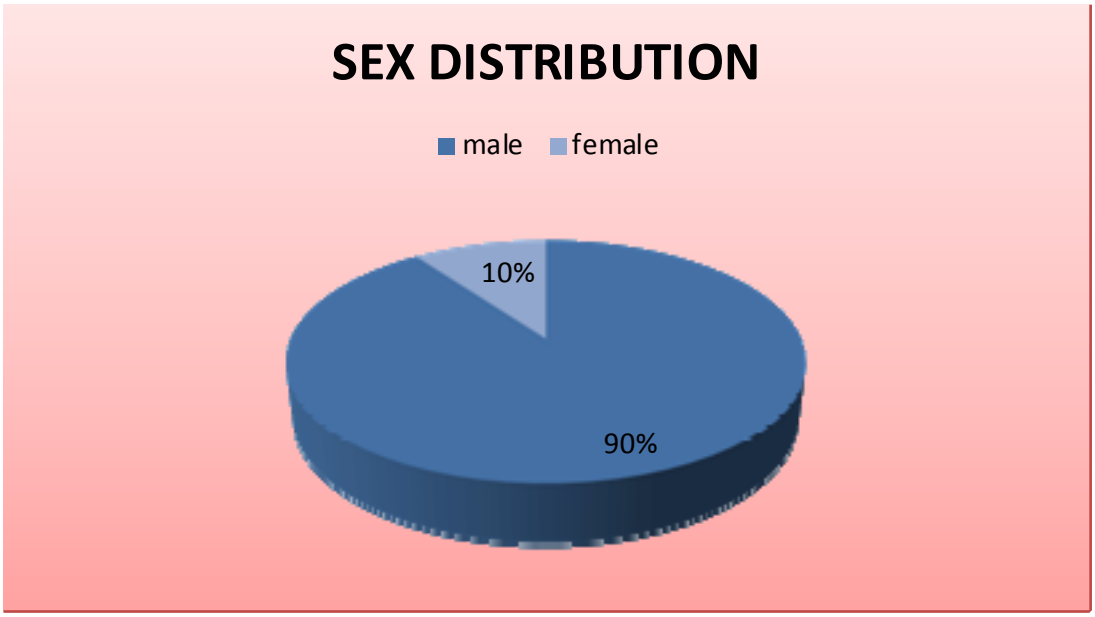
RESULTS

40 consecutive undifferentiated spondyloarthropathy patients were examined clinically, investigated and followed up for one year to assess their outcome.

Sex Distribution

Among the 40 patients of the study, 36 (90%) were males and 4 (10%) were females.

Sex	Total No. (%)
Male	36 (90%)
Female	4(10%)



Age

The mean age of the patients was 30.2 years with the range between 20 and 47 years.

Age at onset of disease

Among the 40 patients, the mean age at onset of the disease was 28.4 years with the range between 17 and 45 years.

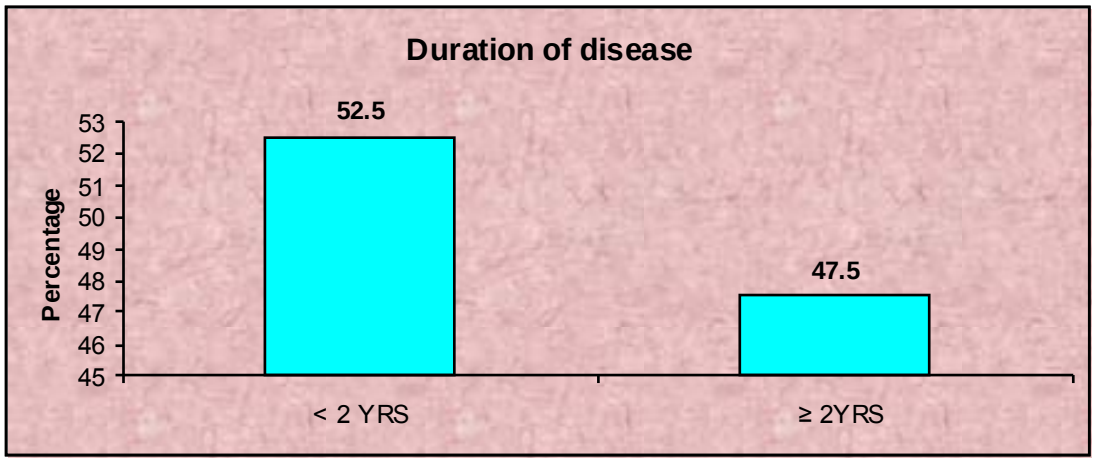
SEX	Mean age at onset	Std. Deviation
Male	28.03	7.894
Female	32.00	6.683

The p value is 0.340 (statistically not significant). There is no significant difference in the mean age at onset of the condition /disease between male and female.

Duration of disease

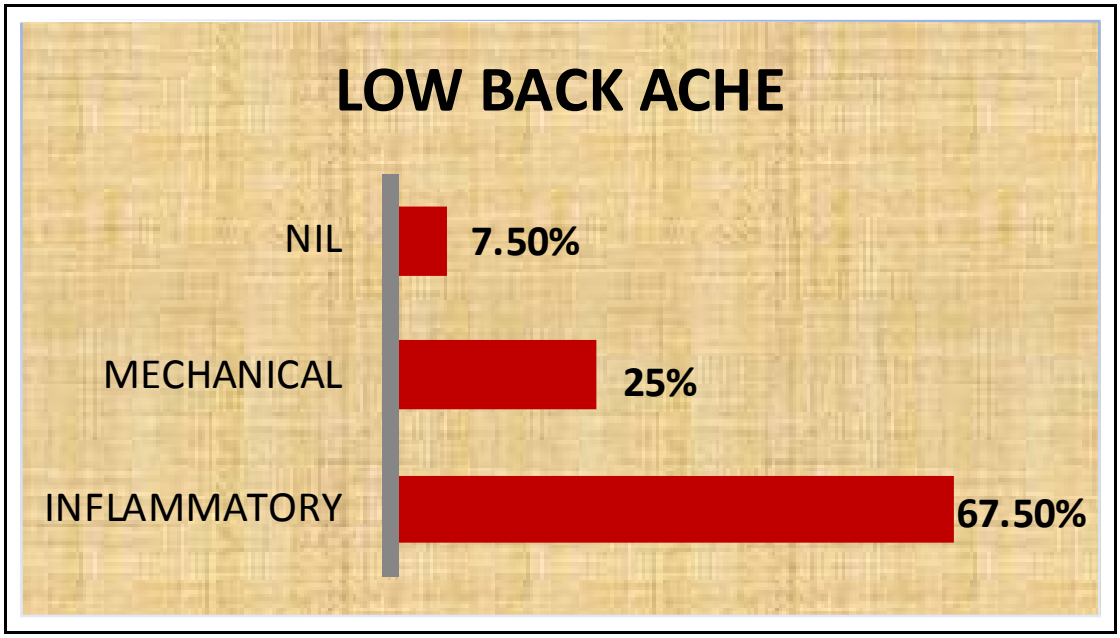
The duration of the disease ranges between 3 months and 6 years. The median duration of the disease was 15 months. The mean duration of the disease was 22.7 months.

Duration	Number of Patients	Percentage
< 2 YRS	21	52.5
≥ 2YRS	19	47.5
TOTAL	40	100



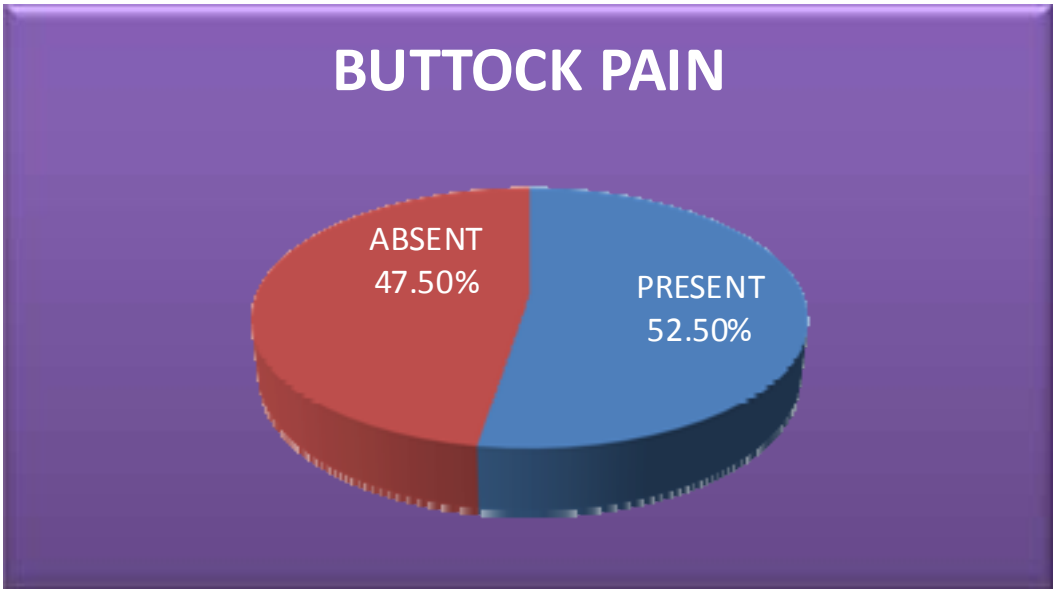
Back ache

Among the 40 patients, 27 (67.5%) had inflammatory back ache, 10 patients (25%) had mechanical back ache and 3 patients (7.5%) had no back ache at the time of presentation.



Buttock Pain

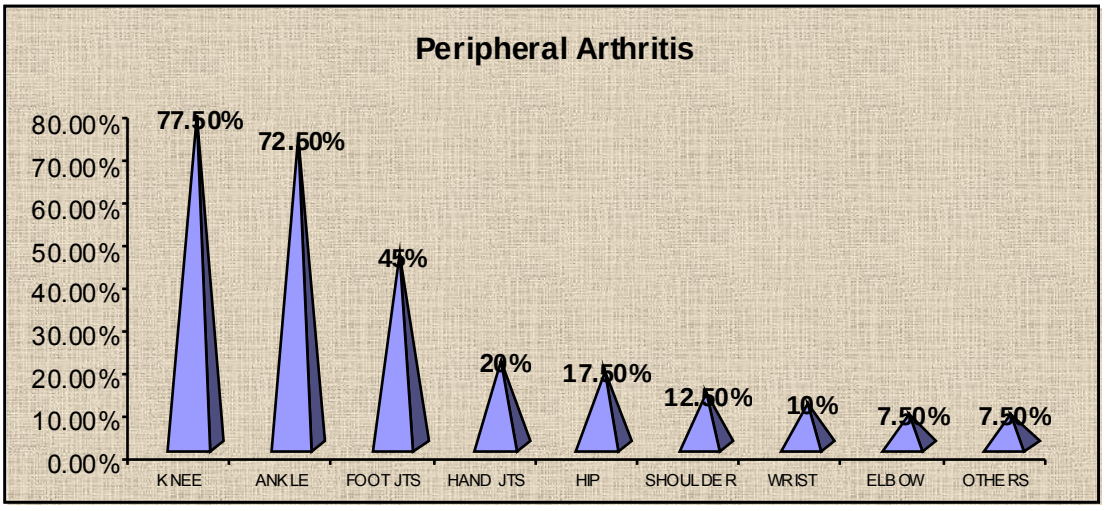
Among the 40 patients, 21 patients (52.5%) had buttock pain and 19 (47.5%) had no buttock pain.



Peripheral Arthritis

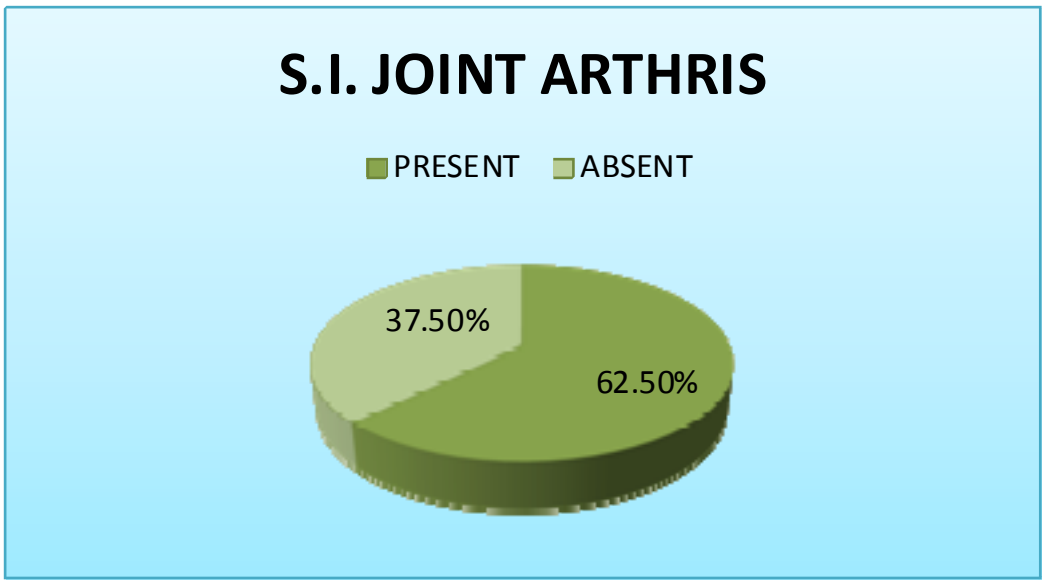
Among the 40 patients, 38 (95%) had peripheral arthritis and 2 (5%) had no evidence of peripheral arthritis. 31 patients (77.5%) had knee arthritis, 29 (72.5%) had ankle arthritis, 18 (45%) had foot joints involvement, 8 (20%) had hand joints involvement, 7 (17.5%) had hip joint involvement, 5 (12.5%) had shoulder arthritis 4 (10%) had wrist arthritis and 3 (7.5%) had elbow joint involvement. 3 patients (7.5%) had other joints involvement (acromioclavicular jt, manubriosternal jt, sternoclavicular jt).

Arthritis	No.of Patients	% of Involvement
KNEE	31	77.50%
ANKLE	29	72.50%
FOOT JTS	18	45%
HAND JTS	8	20%
HIP	7	17.5%
SHOULDER	5	12.5%
WRIST	4	10%
ELBOW	3	7.5%
OTHERS	3	7.5%



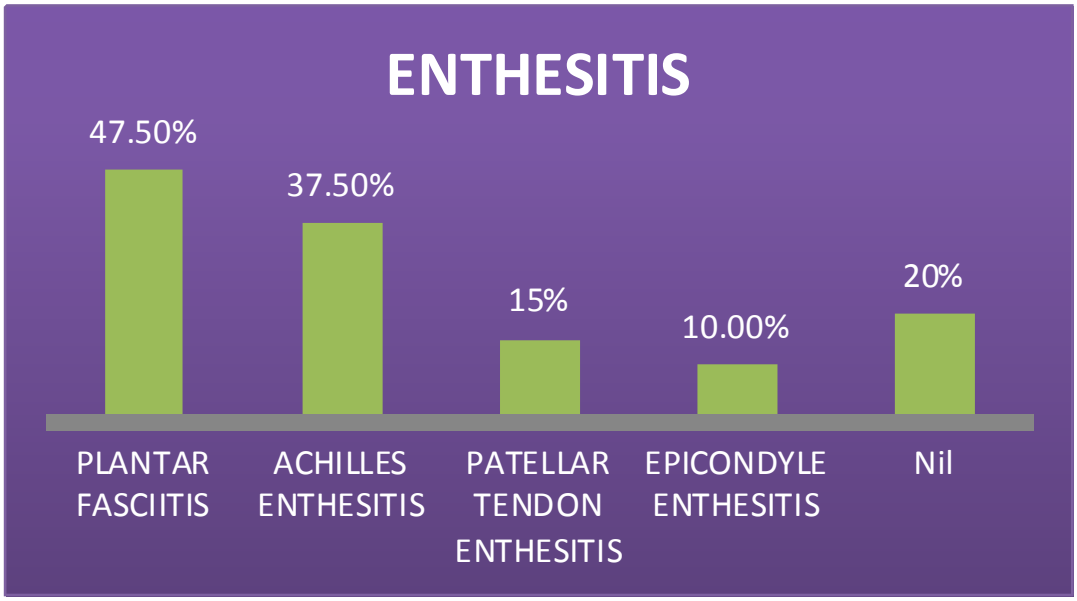
Sacro Iliac Joint Arthritis

Among the study group, 25 patients (62.5%) had S.I. joint involvement and 15 patients (37.5%) had no S.I. joint involvement at the time of presentation.



Enthesitis

32 patients (80%) had enthesitis and 18 (20%) had no enthesitis. Among them, 19 (47.5%) had plantar fasciitis, 15 (37.5%) had Achilles tendon enthesitis, 4(10%) had epicondyle enthesitis and 6 (15%) patients had patellar tendon enthesitis.



Dactylitis

In our study, dactylitis was seen in 5 (12.5%) patients and absent in 35 (87.5%) patients.

Uveitis

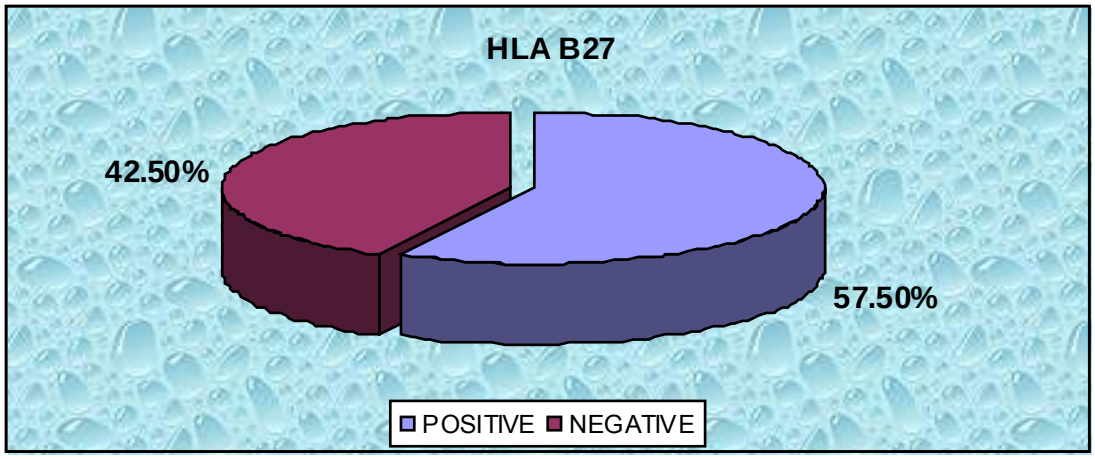
Among the 40 patients, uveitis was seen in 2 (5%) patients.

Family history

Positive family history was seen in only one patient (2.5%) among the 40 patients .

HLA B27

HLA B27 was positive in 23 (57.5%) patients and negative in 17 (42.5%) patients



ESR

ESR was elevated in 29 (72.5%) patients and was normal in 11 (27.5%) patients. The mean ESR was 52.8.

Mean	52.8
Median	42.5
Mode	40
Std .deviation	37.07
Range	125
Minimum	5
Maximum	130

ESR	*REMAINED AS uSpA*	*PROG. TO AS/PsA*
Elevated	24 (82.8%)	5 (17.2%)
Normal	9 (81.8%)	2 (18.2%)

The p value is 1.0 which is not significant.

CRP

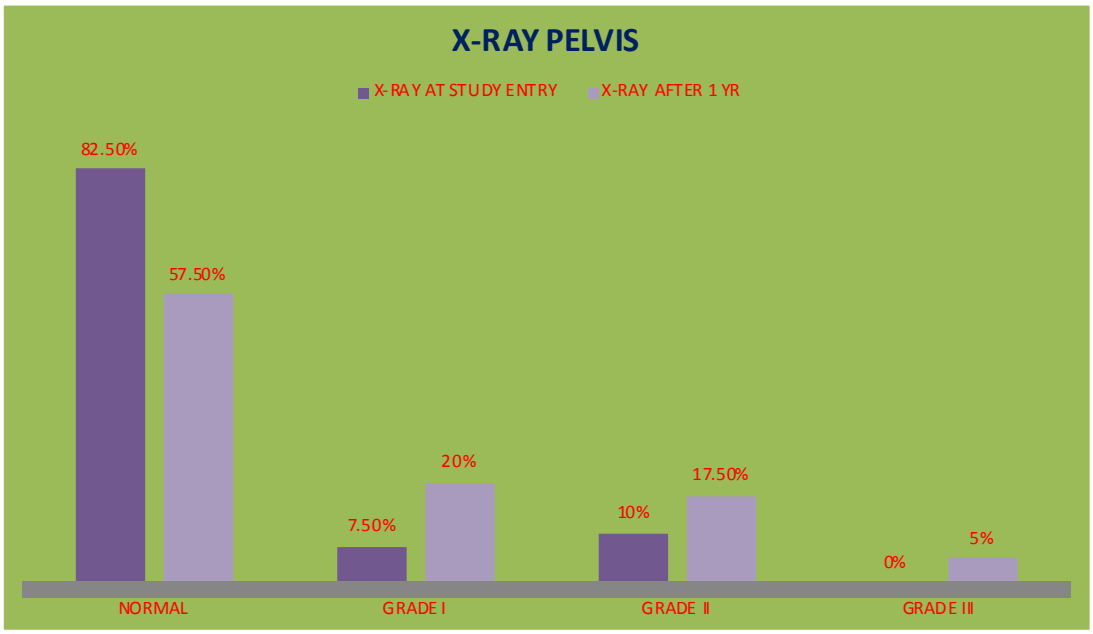
Among the 40 patients, CRP was positive in 27 (67.5%) patients and negative in 13 (32.5%) patients.

CRP	*REMAINED AS uSpA*	*PROG. TO AS/PsA*
Elevated	22 (81.5%)	5 (18.5%)
Normal	11 (84.6%)	2 (15.4%)

X-RAY PELVIS

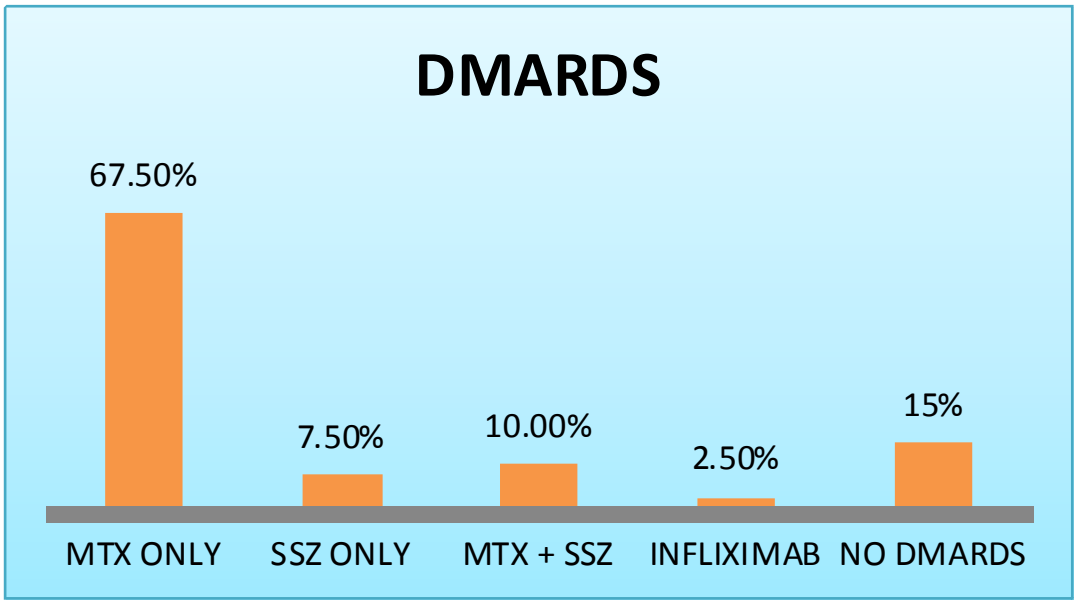
X-ray pelvis was taken at the time of presentation and repeated after one year. At the time of presentation, 33 patients (82.5%) had normal X-ray, 3 (7.5%) had grade I changes and 4 (10%) had grade II changes.

After 1 yr follow up, 23 patients (57.5%) had normal X-ray, 8 (20%) had grade I changes, 7(17.5%) had grade II changes and 2 (5%) had grade III changes.



DMARDS

Among the 40 patients, DMARDS therapy was started in 34 (85%) patients and 6 (15%) were not on these drugs. Among the patients on DMARDS, 27 (67.5%) were on Methotrexate alone, 3 (7.5%) were on Sulfasalazine alone, 4 (10%) were on both these drugs and 1(2.5%) patient was given Infliximab.



BASDAI:

The mean BASDAI at study entry was 6.2 and after one year was 3.1.

BASFI

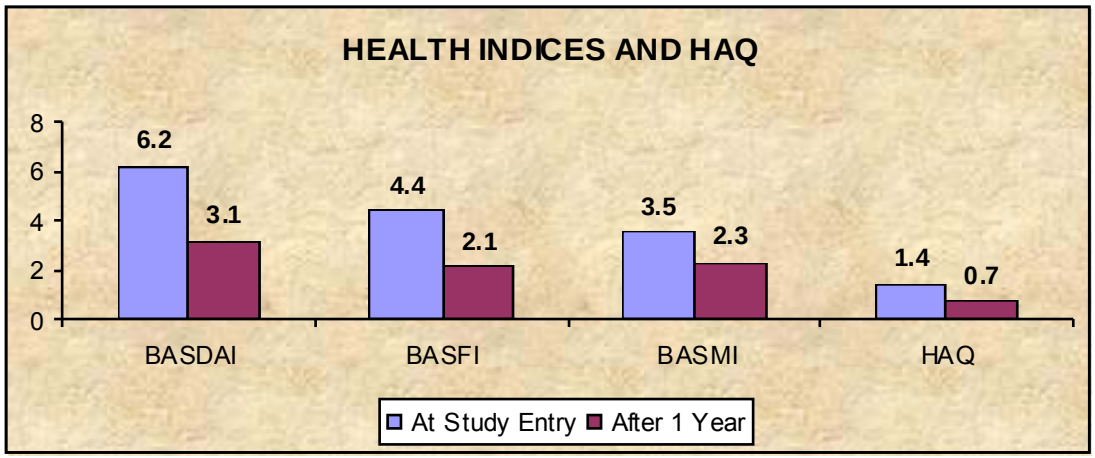
The mean BASFI at study entry was 4.4 and after one year was 2.1.

BASMI

The mean BASMI at study entry was 3.5 and after one year was 2.3.

HAQ

The mean HAQ score at study entry was 1.36 and after one year was 0.7



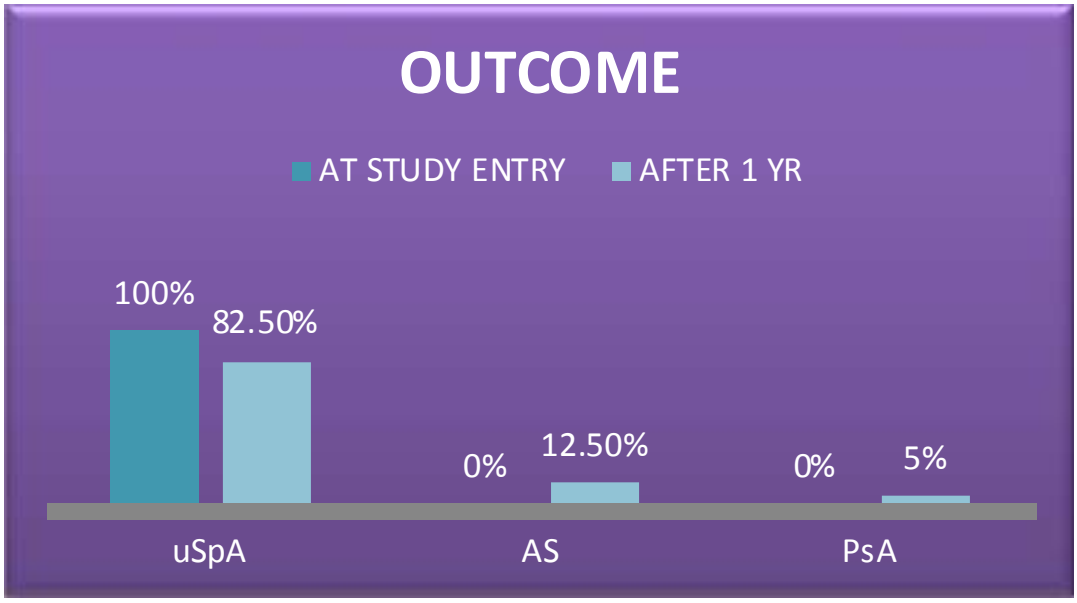
Correlation between HLA B27 and health indices

INDICES (At study entry)	HLA B27	No. OF PATIENTS	MEAN	STD.DEV	P VALUE
BASDAI 1	Positive	23	6.55	.939	0.034
	Negative	17	5.80	1.223	
BASFI 1	Positive	23	4.41	1.007	0.772
	Negative	17	4.31	1.077	
BASMI 1	Positive	23	3.54	.686	0.411
	Negative	17	3.35	.755	
HAQ 1	Positive	23	1.37	.124	0.720
	Negative	17	1.35	.167	

The mean score value of BASDAI 1 is significantly (p =0.034) higher in HLA B27 positive group compare to negative group.In the other health indices there is no signicant difference in the mean score between positive and negative group of HLA B27.

Outcome

Of the 40 patients, 33 (82.5%) patients remained as undifferentiated spondyloarthropathy, 5 (12.5%) patients progressed to ankylosing spondylitis and 2 (5%) patients progressed to psoriatic arthritis after one year of follow up.



Correlation between HLA B27 and outcome

HLA B27	Outcome-uSpA	Outcome - AS + PsA
Positive	16	7
Negative	17	0

This is statistically significant, p value is 0.014. This shows that there is a significant association between HLA B27 and progression to AS.

Correlation between duration and outcome

Duration	Outcome - uSpA	Outcome - AS+PsA
<2 yrs	21	0
$\geq$ 2yrs	12	7

This is statistically significant, p value is 0.003. This indicates that the chance of progression to AS/ PsA is significantly higher in patients with disease duration $\geq$ 2 years.

Hip involvement and progression to ankylosing spondylitis

Hip Involvement	*Outcome - AS*	*Outcome – uSpA*
Present	4	3
Absent	1	32

This is statistically significant, p value is 0.000957. This table shows that hip involvement is associated with progression to AS.

DISCUSSION

40 consecutive patients suffering from undifferentiated spondyloarthropathy were taken up for the study to assess their clinical presentation and to study their outcome after one year.

Among the 40 patients, the mean age at onset of the disease was 28.4 years with the range between 17 and 45 years. This is in comparison with a Brazilian study by Sampaio Barros et al., (111 patients followed up for 10 years), where the mean age at onset was 27.2 years[34]. In an Indian study by Kumar et al. (22 patients followed up for 11 yrs), the mean age at onset was 17 years with the range between 8 to 39 years.[33] The correlation between the mean age of onset and the sex was not significant.

In this study, 36 (90%) were males and 4 (10%) were females which was in similar with another Indian study by Kumar et al., where 19 (86.4%) were males and 3(13.6%) were females.[33] In the Brazilian study by Sampaio Barros et al., there were 90 (81.1%) men and 21 (18.9%) were women.[34]

In this study, the duration of the disease ranges between 3 months and 6 years and the mean duration of the disease was 22.7 months unlike the Indian study by Kumar et al., where the mean duration of the disease was 8 months with the range between 4 and 24 months.[33]21 patients (52.5%) had disease duration less than 2 years and 19 patients (47.5%) with duration more than or equal to 2 years. All the patients who progressed to ankylosing spondylitis/psoriatic arthritis had a disease duration of two or more years and this is statistically significant (p value 0.003).

Of the 40 patients, 27 (67.5%) had inflammatory back ache, 10 patients (25%) had mechanical back ache and 3 patients (7.5%) had no back ache at the time of presentation. In contrast, in Kumar et al. study, inflammatory back ache was present in 100% of the patients[33] and in Sampaio Barros et al. study, inflammatory back ache was present in 28.8% patients.[34]

In this study, buttock pain was present in 21 patients (52.5%). In Kumar et al. study, buttock pain was seen in 77% of the patients. Sampaio Barros et al. study showed a less prevalence of buttock pain (8.1%) at the time of presentation.[34]

Among the 40 patients, 38 (95%) had peripheral arthritis and 2 (5%) had no evidence of peripheral arthritis. The pattern of peripheral joint involvement is as follows : knee joints – 31 patients(77.5%), ankle joints – 29(72.5%), foot joints – 18 (45%), hand joints – 8 (20%), hip joints - 7 (17.5%), shoulder joints - 5 (12.5%), wrist joints - 4 (10%) and elbow joints - 3 (7.5%). 3 patients (7.5%) had other joints involvement (acromioclavicular jt, manubriosternal jt, sternoclavicular jt). Kumar et al. study showed 64% of hip involvement, 18% of shoulder involvement, 77% of ankle involvement, 82% of knee involvement and 50% of hand and wrist joint involvement. [33]Sampaio Barros et al. study showed 28.8% of knee involvement, 35.1% of ankle involvement, 10.8% of hip involvement. Elbow, wrist and shoulder joints were not involved at the time of presentation in the Brazilian study.[34]

Hip involvement was noted initially in 7 patients, of which, 4 progressed to ankylosing spondylitis and this is statistically significant (p value 0.000957).

In our study, 32 patients (80%) had enthesitis. Of these, 19 (47.5%) had plantar fasciitis, 15 (37.5%) had Achilles tendon enthesitis, 4(10%) had epicondyle enthesitis and 6 (15%) patients had patellar tendon enthesitis. In Kumar et al. study, 10 (45%) patients had enthesitis[33] and in Sampaio Barros et al. study, Achilles tendon enthesitis was seen in 10.8% of the patients and plantar fasciitis was seen in 9% of them.[34]

In this study, dactylitis was seen in 5 (12.5%) patients and uveitis was seen in 2 (5%) patients. In Kumar et al. study, uveitis developed in 4 patients (18%).[33]

Positive family history was seen in only one patient (2.5%) in this study. In Kumar et al. study, positive family history was seen in 2 patients (9.1%) [33]and in Sampaio Barros et al. study, 13 patients (11.7%) had positive family history.[34]

HLA B27 was positive in 23 (57.5%) patients and negative in 17 (42.5%) patients which is in contrast to Kumar et al. study, where HLA B27 was positive in 100% of the patients.[33] In Sampaio Barros et al. study, HLA B27 was positive in 61.3% patients.[34] HLA B27 is positive in all patients who progressed to ankylosing spondylitis/psoriatic arthritis and this is statistically significant (p value 0.014). HLA B27 positivity is associated with increased disease activity as evidenced by the statistical significance between HLA B27 and BASDAI at the study entry (p value 0.034). The correlation between HLA B27 and BASFI, BASMI, HAQ at the entry of the study are not statistically significant.

ESR was elevated in 29 (72.5%) patients and was normal in 11 (27.5%) patients. The median ESR was 42.5 with the range between 5 and 130. In the Kumar et al. study, the median ESR was 42 with the range between 15 and 50.[33] Correlation between elevated ESR and the outcome was analysed and found that this correlation is not significant.

Among the 40 patients, CRP was positive in 27 (67.5%) patients and negative in 13 (32.5%) patients. There was no correlation between CRP and outcome of undifferentiated spondyloarthropathy in this study.

In this study, sacroiliac joint was involved clinically in 25 patients (62.5%).

X-ray pelvis was taken at the time of presentation and repeated after one year. At the time of presentation, 33 patients (82.5%) had normal X-ray, 3 (7.5%) had grade I changes and 4 (10%) had grade II changes.

After 1 yr follow up, 23 patients (57.5%) had normal X-ray, 8 (20%) had grade I changes, 7(17.5%) had grade II changes and 2 (5%) had grade III changes. In Kumar et al. study comprising 22 patients, after 11 years of follow up, 7 patients had normal X- ray, 1 patient had B/L grade II sacroiliitis, 13 patients had B/L grade III sacroiliitis and 1 patient had B/L grade IV sacroiliitis.[33]

Of the 40 patients who were enrolled in this study, 33 (82.5%) patients continued to remain as undifferentiated spondyloarthropathy at the end of one year, while 5 (12.5%) patients progressed to ankylosing spondylitis and 2 (5%) patients progressed to psoriatic arthritis. No Indian studies are available

for comparison of outcome of undifferentiated spondyloarthropathy at the end of one year. Sampaio Barros et al. followed 68 patients for two years and in his study 75% patients remained as uSpA, 13% undergone remission, 10% progressed to AS and 2% progressed to PsA.[32] In the Indian study by Kumar et al., 15 (68%) developed ankylosing spondylitis, one developed psoriatic arthritis, four remain undifferentiated, and two had natural remission at the end of 11 yrs.[33] Sampaio Barros et al. found that after a follow up of ten years with 111 patients, 27 (24.3%) patients progressed to AS, 3 (2.7%) patients to PsA while 25 (22.5%) patients went into remission.[34]

CONCLUSION

1) Males preponderence was noted in this one year follow up study of undifferentiated spondyloarthropathy patients.

2) The mean age at onset of the disease was 28.4 years.

3) Involvement of the joints of lower limb appendicular skeleton was noted predominantly in this study.

4) The chance of progression to ankylosing spondylitis/psoriatic arthritis is directly proportional to the duration of the disease.

5) Hip involvement at the time of presentation may predict their progression to ankylosing spondylitis.

6) Significant number of patients had elevation of acute phase reactants, both ESR and CRP.

7) HLA B27 positive patients are more prone for progression to ankylosing spondylitis/psoriatic arthritis.

8) Most of the patients enrolled as undifferentiated spondyloarthropathy at the beginning of this study, continued to remain so at the end of one year follow up.

9) All patients of undifferentiated spondyloarthropathy should be followed up for their progression to ankylosing spondylitis or psoriatic arthritis or inflammatory bowel disease.

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A STUDY ON CLINICAL PROFILE AND OUTCOME OF UNDIFFERENTIATED SPONDYLOARTHROPATHY

Name: Age: Sex: Date:

Address:

RCC No.

H/o. Present Illness:

Past History:

Personal History:

Treatment History:

Family History

General Examination

Pallor:	Icterus	Cyanosis
Clubbing:	Lymphadenopathy:	Pedal Edema
Skin:		
Nails:		
PR:	BP:	

Systemic Examination

CVS:	RS:
Abdomen	CNS

Musculoskeletal System Examination:

INVESTIGATION

Haemogram

Hb:	TC:	DC:
Platelet:	ESR:	

Immunological

CRP:	ASO:	HLA B27:

Bio-Chemistry

Sugar:	Urea:	Creatinine:
Bilirubin:	AST:	ALT:
ALP:	Total Proteins:	Albumin:

Radiography

X-ray Pelvis

BASDAI

BASFI

BASMI

HAQ

BASMI

	0	1	2	3	4	5	6	7	8	9	10	
Tragus to wall (cm)	≤ 10	10– 12.9	13– 15.9	16- 18.9	19– 21.9	22- 24.9	25- 27.9	28- 30.9	31- 33.9	34- 36.9	≥ 37	
Lumbar Flexion (cm)	≥ 7.0	6.4- 7.0	5.7- 6.3	5.0- 5.6	4.3- 4.9	3.6- 4.2	2.9- 3.5	2.2- 2.8	1.5- 2.1	0.8- 1.4	≤ 0.7	
Intermalleolar distance (cm)	≥ 120	110- 119.9	100- 109.9	90- 99.9	80- 89.9	70- 79.9	60- 69.9	50- 59.9	40- 49.9	30- 39.9	≤ 30	
Cervical Rotation (degrees)	≥ 85	76.6- 85	68.1- 76.5	59.6- 68	51.1- 59.5	42.6- 51	34.1- 42.5	25.6- 34	17.1- 25.5	8.6- 17	≤ 8.5	
Lumbar Side Flexion (cm)	≥ 20	18- 20	15.9- 17.9	13.8- 15.8	11.7- 13.7	9.6- 11.6	7.5- 9.5	5.4- 7.4	3.3- 5.3	1.2- 3.2	≤ 1.2	

BASMI (average of 5 scores)

BASDAI

Please place a mark on each line below to indicate your answer to each question relating to **the past week**

1. How would you describe the overall level of **fatigue/tiredness** you have experienced?

   NONE _____ VERY SEVERE

2. How would you describe the overall level of AS **neck, back or hip pain** you have had?

   NONE _____ VERY SEVERE

3. How would you describe the overall level of pain/swelling in joints other than **neck, back, hips** you have had?

   NONE _____ VERY SEVERE

4. How would you describe the overall level of **discomfort** you have had from any areas tender to touch or pressure?

   NONE _____ VERY SEVERE

5. How would you describe the overall level of **morning stiffness** you have had **from the time you wake up?**

   NONE _____ VERY SEVERE

6. How long does your morning stiffness last from the time you wake up?

   _____
   0 hrs ½ 1 1½ 2 or more hours

BASDAI= (Sum of questions 1 to 4 + mean of questions 5 and 6) divided by 5.

BASFI

Bath Ankylosing Spondylitis Functional Index*
BASFI

Date_____ Patient Name_____

Please draw a mark on each line below to indicate your ability with each of the following activities, during the <u>past week:</u>

1. Putting on your socks or tights without help or aids (e.g. sock aids)?

EASY —— **IMPOSSIBLE**
0 10

2. Bending forward from the waist to pick up a pen from the floor without an aid?

EASY —— **IMPOSSIBLE**
0 10

3. Reaching up to a high shelf without help or aids (e.g. helping hand)?

EASY —— **IMPOSSIBLE**
0 10

4. Getting up out of an armless dining room chair without using your hands or any other help?

EASY —— **IMPOSSIBLE**
0 10

5. Getting up off the floor without any help from lying on your back?

EASY —— **IMPOSSIBLE**
0 10

6. Standing unsupported for 10 minutes without discomfort?

EASY —— **IMPOSSIBLE**
0 10

7. Climbing 12-15 steps without using a handrail or walking aid (one foot on each step)?

EASY —— **IMPOSSIBLE**
0 10

8. Looking over your shoulder without turning your body?

EASY —— **IMPOSSIBLE**
0 10

9. Doing physically demanding activities (e.g. physiotherapy exercises, gardening or sports)?

EASY —— **IMPOSSIBLE**
0 10

10. Doing a full day activities whether it be at home or work?

EASY —— **IMPOSSIBLE**
0 10

BASFI= Average of 10 score

INDIAN HAQ

Activity of daily living (ADL): Are you able to:	Without any difficulty	With some difficulty	With much difficulty	Unable to do
	0	1	2	3
Dress yourself, including tying sari/salwar/ dhoti/pyjama and doing buttons?				
Get in and out of bed?				
Lift a full cup or glass to your mouth?				
Walk outdoors on flat ground?				
Wash and dry your entire body?				
Squat in the toilet or sit cross- legged on the floor?				
Bend down to pick up clothing from the door				
Turn a tap on and off?				
Get in and out of autorickshaw/manual rickshaw/car?				
Walk three kilometrcs?				
Shop in a vegetable market?				
Climb a flight of stairs?				

Disability Index = Sum of all scores divided by 12

PATIENT CONSENT FORM

Study Title: A study on Clinical Profile and Outcome of Undifferentiated Spondyloarthropathy

Participant Name: Date:

Age: RCC.No:

Sex:

The details of the study have been provided to me in writing and explained to me in my own language.

I confirm that I have understood the above study and had the opportunity to ask questions.

I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected.

I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).

I have been given an information sheet giving details of the study. I fully consent to participate in the above study.

Signature of the participant

<u>ஆராய்ச்சி ஒப்புதல் படிவம்</u>

ஆராய்ச்சி தலைப்பு

"முதுகெலும்பு அழற்சி நோயின் தன்மை குறித்த ஆய்வு"

ஆராய்ச்சி நிலையம் : மூட்டு, தசை மற்றும் இணைப்புத்திசு
நோய்களியல் துறை,
சென்னை மருத்துவக் கல்லூரி மற்றும்
ராஜீவ் காந்தி அரசு பொது மருத்துவமனை, சென்னை.

பங்கு பெறுவரின் பெயர் :

பாலினம் :

பங்குபெறபவரின் எண் :

பங்கு பெறுபவர் இதனை (✓) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கின்றேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிகிறேன். எனது உடல் நலம்பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கதிற்கு மாறான நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்து அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன். ☐

இந்த ஆய்வில் எனக்கு இரத்தம், சிறுநீர், எக்ஸ்ரே, ஸ்கேன் மற்றும் தசை பரிசோதனை செய்துகொள்ள நான் முழு மனதுடன் சம்மதிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் ..... இடம்..... தேதி.....

கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம்..... தேதி.....

ஆய்வாளரின் பெயர் .....

S. No	NAME	AGE AT ONSET (in years)	AGE	SEX	RCC NO	DURATION (in months)	LOW BACK ACHE	BUTTOCK PAIN	PERIPHERAL ARTHRITIS AT STUDY ENTRTY
1	Shankar	35	35	male	54535	3	mechanical	+	Rt.shoulder,Lt.ankle,midtarsal jt
2	Rahuman	32	36	male	53281	48	inflammatory	+	-
3	Santhana kumar	34	34	male	53600	6	inflammatory	-	Rt.wrist,Lt.hip,Lt.knee,Rt.ankle,Rt.midtarsal/subtalar jts
4	Vijayasarathy	26	30	male	51603	48	inflammatory	+	Rt. shoulder,Rt. hip,B/L knee jts
5	Saravanan	27	30	male	53639	30	mechanical	+	B/L ankle,midtarsal and subtalar jts
6	Arul kumar	24	28	male	48155	48	inflammatory	-	Rt hip,Lt knee jt
7	Devaraj	29	31	male	53951	24	inflammatory	+	-
8	Ibrahim	30	32	male	54091	24	inflammatory	+	B/L knee,ankle jts
9	Manikandan	21	21	male	53293	6	inflammatory	-	Rt.3rd PIP/DIP jt,Lt.4th PIP/DIP jts,B/L acromioclavicular jts,Lt.ankle jt
10	Simon	24	24	male	54200	5	inflammatory	-	Lt.knee/ankle/midtarsal jts
11	Durai	20	23	male	50361	36	inflammatory	-	Lt.elbow,B/L knee,ankle,Rt.midtarsal/subtalar jts
12	Damodharan	29	35	male	51856	72	inflammatory	+	B/L IP jt thumb,Lt.2nd PIP/DIP jts,B/L knee jts
13	Sundararajan	40	45	male	53782	60	mechanical	-	Rt.knee,Lt.ankle jts
14	Subramani	25	25	male	53223	6	inflammatory	+	Lt.knee,B/L ankle,Rt.subtalar jts
15	Vetriselvan	20	20	male	53594	10	mechanical	-	Lt.wrist/3rd PIP/DIP jts,B/L knee/ankle/midtarsal/MTP jts
16	Haribabu	23	23	male	53746	3	-	+	B/L knee/ankle jts
17	Kumaran	43	45	male	53947	15	inflammatory	-	Lt.knee/ankle jts
18	Narayanasamy	20	20	male	53622	6	inflammatory	-	B/L elbow/knee/midtarsal jts
19	Varadaraj	42	47	male	53589	60	mechanical	+	Rt.hip,Lt.ankle/midtarsal jts
20	Ilavarasan	21	21	male	53990	4	inflammatory	+	Rt.ankle/midtarsal/subtalar jts
21	JafferAli	17	21	male	54133	48	inflammatory	+	Rt.hip,Lt.knee/ankle/4th MTP jt
22	Mahalingam	39	39	male	53327	9	inflammatory	+	Rt.hip/wrist,Lt.midtarsal/subtalar jts
23	Arumugam	24	25	male	53436	12	inflammatory	+	B/L knee,Rt.3rd PIP/DIP jts,manubriosternal jt
24	Mahendran	23	26	male	50041	36	inflammatory	-	Lt.sternoclavicular jt,Rt.wrist,B/L knee/ankle jts
25	Paapukumar	23	24	male	53091	12	inflammatory	-	B/L knee/midtarsal jts
26	Rajendran	27	30	male	53633	36	mechanical	-	Rt.knee,Lt.ankle jts
27	Venkatesan	19	22	male	51808	36	-	-	B/L knee/ankle jts
28	Selvakumar	19	21	male	51933	15	mechanical	-	Rt.shoulder/3rd PIP jt,Lt.knee,Rt.5th MTP/PIP jts,Rt.SC jt.
29	Kamaraj	20	20	male	53049	6	inflammatory	+	B/L knee/ankle jts
30	Hari	27	27	male	53360	3	-	+	B/L knee/ankle/subtalar/midtarsal/2nd,3rd MTP jts
31	Radha	26	26	female	54192	3	inflammatory	+	B/L ankle/midtarsal jts
32	Ezhilarasi	33	35	female	53369	24	mechanical	+	Lt.knee,B/L ankle jts
33	Kanagamani	41	43	female	54304	24	inflammatory	-	B/L knee/ankle jts

S. No	NAME	AGE AT ONSET (in years)	AGE	SEX	RCC NO	DURATION (in months)	LOW BACK ACHE	BUTTOCK PAIN	PERIPHERAL ARTHRITIS AT STUDY ENTRTY
34	Lakshmi	28	32	female	54374	48	mechanical	-	Lt.3rd PIP jt,B/L knee/ankle/midtarsal jts
35	Sahayaraj	45	45	male	54121	7	inflammatory	+	Lt.knee,B/L ankle jts
36	Nageswar Rao	25	25	male	53260	9	inflammatory	-	Lt.knee,3rd MCP/PIP/DIP jts
37	Kumar	30	32	male	51962	15	inflammatory	-	B/L shoulder/elbow/knee/ankle jts
38	Tamilmani	26	28	male	52106	24	inflammatory	+	Rt.shoulder/1,2,3,4 PIP jts/knee,Lt.ankle jt
39	Ramesh	37	37	male	54376	3	mechanical	-	B/L knee/ankle/midtarsal jts
40	Selvamani	43	45	male	50074	24	inflammatory	+	Lt.hip,B/L knee/ankle jts

S.I. JT	SCHOBER TEST	ENTHESITIS AT STUDY ENTRY	UVEITIS	DACTYLITIS	FAMILY HISTORY	HLA B27	ESR (mm/hr)	CRP (mg/L)	ASO (IU/L)
-	5 cm	B/L achilles	-	-	-	-	45	>6	-
+	4 cm	B/L achilles	-	-	-	-	11	-	-
+	3 cm	Rt achilles,Rt plantar fasciitis	-	-	-	+	120	6	200
+	3 cm	B/L plantar fasciitis	-	-	-	+	45	>6	200
-	3 cm	-	-	-	-	+	18	6	-
+	2.5 cm	Lt achilles,Rt medial epicondyle enthesitis	RE-ant.uveitis	-	-	+	14	>6	-
+	3 cm	B/L plantar fasciitis, achilles enthesitis, Lt.patellar tendon enthesitis	-	-	-	+	11	-	200
-	3 cm	-	-	-	-	+	10	6	-
+	3 cm	Lt.Achilles enthesitis	-	Lt.4th toe	-	-	71	-	-
+	3 cm	Lt.patellar tendon enthesitis,B/L plantar fasciitis	-	-	-	+	30	>6	-
-	2.5 cm	B/L medial epicondyle enthesitis,B/L Achilles enthesitis	-	-	-	+	100	>6	-
+	1.5 cm	B/L Achilles enthesitis,B/L plantar fasciitis	-	Lt.2nd toe	-	+	30	-	-
-	1.5 cm	Lt.plantar fasciitis	-	-	-	-	20	-	-
+	2 cm	-	-	-	-	+	130	>6	200
+	2 cm	Rt.lateral epicondyle enthesitis,Lt.plantar fasciitis	-	Lt.3rd finger	-	+	85	6	-
-	5 cm	-	-	-	-	-	60	6	-
-	2 cm	Lt.Achilles enthesitis	-	-	-	+	40	-	-
+	1.5 cm	Rt.plantar fasciitis,Rt.patellar tendon enthesitis	-	-	-	-	100	6	200
+	2 cm	-	-	-	-	-	15	-	-
+	2.5 cm	Rt.plantar fasciitis, Rt.Achilles enthesitis	-	-	-	+	60	-	-
+	3 cm	Lt.Achilles enthesitis	RE-old ant.uveitis,LE ant.uveitis	-	-	+	40	6	-
-	3 cm	Lt.Achilles enthesitis	-	-	-	+	88	>6	400
+	3 cm	-	-	Rt.3rd toe	-	+	26	>6	-
-	1.5 cm	B/L plantar fasciitis	-	-	-	-	51	6	-
-	5 cm	B/L plantar fasciitis	-	-	-	-	5	-	200
+	2 cm	Lt.lateral epicondyle enthesitis,Lt.plantar fasciitis	-	-	-	-	15	-	-
-	4.5 cm	B/L patellar tendon enthesitis	-	-	-	-	40	-	-
+	2.5 cm	B/L plantar fasciitis	-	-	-	+	87	>6	-
-	1.5 cm	-	-	-	-	+	62	6	-
-	3 cm	Rt.Achilles enthesitis	-	-	-	-	5	6	-
+	2 cm	B/L plantar fasciitis	-	-	-	-	112	6	200
+	2 cm	Lt.plantar fasciitis	-	-	-	+	48	>6	-
+	2.5 cm	Lt.patellar tendon enthesitis	-	-	-	+	38	-	-

S.I. JT	SCHOBER TEST	ENTHESITIS AT STUDY ENTRY	UVEITIS	DACTYLITIS	FAMILY HISTORY	HLA B27	ESR (mm/hr)	CRP (mg/L)	ASO (IU/L)
+	1.5 cm	Lt.Achilles enthesitis	-	-	-	-	25	-	-
+	2.5 cm	B/L plantar fasciitis	-	-	-	-	85	6	-
+	1.5 cm	Rt.plantar fasciitis	-	Lt.3rd finger	-	+	125	>6	-
-	2.5 cm	Rt.plantar fasciitis	-	-	-	-	40	>6	-
+	2 cm	Lt.plantar fasciitis, Lt.Achilles enthesitis	-	-	+	+	110	>6	-
-	2.5 cm	B/L patellar tendon enthesitis	-	-	-	-	20	>6	-
+	2.5 cm	-	-	-	-	+	75	6	-

X RAY1	X RAY2	DMARDS	BASDAI 1	BASDAI 2	BASFI 1	BASFI 2	BASMI 1	BASMI2	HAQ 1	HAQ 2	OUTCOME
normal	normal	-	2.6	1.6	2	1.3	3	2.6	1.16	0.58	uSpA
normal	normal	-	4.4	3.8	3.9	2	3.3	3	1.58	0.67	uSpA
normal	Rt.grade I	MTX	7.6	5	6.1	4.4	3.7	3.1	1.5	1.08	uSpA
Rt grade I	B/L grade II	MTX	6	7.9	1.9	2.8	3.4	4.2	1.42	1.58	AS
normal	normal	MTX	6.2	2.6	3.3	1	3.2	2.3	1.25	0.5	uSpA
Rt.grade II	Rt grade III,Lt grade II	MTX	4	4.2	3.7	3.8	2.6	2.5	1.33	1.16	AS
normal	normal	MTX	6.8	2	3.2	0.9	3.5	2.6	1.16	0.5	PsA
normal	Rt grade I	MTX	5	3.8	4.1	3.2	2.8	2.2	1.5	1	uSpA
normal	Rt grade I	SSZ	6.8	4.6	4.1	3.2	4.3	3.4	1.58	1.08	uSpA
normal	normal	MTX	7	3	4.7	1.9	3	2.3	1.5	0.58	uSpA
normal	Lt grade II	MTX,SSZ	6.1	3.8	4.3	1.4	3.8	2	1.58	0.5	uSpA
normal	Lt grade I	MTX	5.9	3	4.3	1.3	4.3	3	1.33	0.5	PsA
normal	normal	MTX	5.3	1.2	3.9	1.2	4.1	2.9	1.5	0.58	uSpA
normal	normal	MTX	7.6	5.6	5.4	3.3	4.1	2.8	1.33	0.91	uSpA
normal	Rt grade I	MTX	8.4	0.6	6.1	1.2	4.3	1.9	1.67	0.25	uSpA
normal	normal	MTX	5.4	1	4.9	0.8	2.1	1.8	1.5	0.33	uSpA
Lt grade II	Lt grade II	MTX	6.9	1	5.9	0.6	3.3	1.5	1.25	0.42	uSpA
normal	normal	MTX	7.6	1.4	5.1	0.8	3.8	1.7	1.58	0.33	uSpA
normal	normal	-	6.8	7	4.9	5.4	3.7	3.9	1.08	1.5	uSpA
Rt grade II	Rt grade II	MTX	6.7	7.2	5.1	5.2	3.6	3.7	1.33	1.58	uSpA
Rt grade I	B/L grade II	MTX	6.1	4.2	4	3.2	1.8	1.6	1.25	1	AS
normal	normal	SSZ	6.6	1.2	4.5	1.4	3.2	1.2	1.42	0.5	uSpA
normal	Rt grade I	SSZ	6.2	4.8	3.6	2.4	2.8	1.8	1.42	1.08	uSpA
normal	normal	MTX	7.2	3	6.6	2.3	4.2	2.1	1.42	0.42	uSpA
normal	normal	-	4.8	1	2.7	1	2.1	1.7	1.25	0.33	uSpA
normal	normal	-	6.6	4.4	4.4	2.9	3.3	2.1	1.25	0.83	uSpA
normal	normal	-	5.8	1.8	5	1.3	2.1	2	1.25	0.42	uSpA
normal	normal	MTX	6.4	4.3	4	2.8	3.5	2.7	1.33	0.91	uSpA
normal	normal	MTX	6.8	2.6	4.5	1.4	4.3	2.4	1.33	0.5	uSpA
normal	Rt grade I	MTX	5.2	1.6	3.9	1.5	2.5	1.7	1.16	0.33	uSpA
normal	normal	MTX,SSZ	7	4.1	5	3.4	3.8	2.7	1.42	1.08	uSpA
Lt grade I	Lt grade II	MTX	7.6	4.3	5.2	3.7	3.6	2.8	1.25	0.91	uSpA
normal	normal	MTX	7	2.2	5	1.7	3.7	2.2	1.25	0.58	uSpA

BASDAI-1, BASFI-1, BASMI-1, HAQ-1: At study Entry

BASDAI-2, BASFI-2, BASMI-2, HAQ-2: After One Year

X RAY1	X RAY2	DMARDS	BASDAI 1	BASDAI 2	BASFI 1	BASFI 2	BASMI 1	BASMI2	HAQ 1	HAQ 2	OUTCOME
normal	normal	MTX	5.9	1.8	3.7	1.6	4.2	2.5	1.42	0.5	uSpA
normal	Lt grade I	MTX	5.4	1.8	5.6	1.5	3.5	1.7	1.16	0.33	uSpA
normal	normal	MTX	6.8	1.6	3.8	0.9	4.1	1.5	1.25	0.42	uSpA
normal	normal	MTX	5.4	2.6	3.8	1.3	3.7	2	1.25	0.42	uSpA
Lt grade II	Lt grade III	MTX,SSZ,Infliximab	7.4	2.2	5	0.9	5	1.4	1.42	0.17	AS
normal	normal	MTX	6.4	1.4	3.8	1.3	3.3	1.8	1.42	0.5	uSpA
normal	B/L grade II	MTX,SSZ	5.6	4.1	3.7	2.6	3.9	2.6	1.42	1	AS

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

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Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. I. Venkatesh
PG in DM Rheumatology
Madras Medical College , Ch-3

Dear Dr. I. Venkatesh

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the proposal entitled " A study on clinical profile and outcome of Undifferentiated Spondyloarthropathy" No. 24012011.

The following members of Ethics Committee were present in the meeting held on 28.01.2011 conducted at Madras Medical College, Chennai -3.

1. Prof. S.K. Rajan, MD	– Chairperson
2. Prof. A. Sundaram, MD Dean i/c , Madras Medical College, Chennai -3	– Member Secretary
3. Prof R. Sathianathan Director , Institute of Psychiatry, MMC,Ch-3	– Member
4. Prof R. Nandhini, MD Director, Institute of Pharmacology, MMC, Ch-3	– Member
5. Prof. Geetha Subramanian, MD,DM Prof. & Head , Dept. of Cardiology, MMC, Ch-3	– Member
6. Prof. Md. Ali, MD, DM Professor & Head ,,Dept. of MGE, MMC, Ch-3	– Member
7. Thiru. T.S. Bharathidasan Administrative Officer, MMC, Chennai -3	– Layperson
8. Thiru. S. Govindasamy . BA.BL	– Lawyer
9. Tmt. Arnold Soulina	– Social Scientist

We approve the Proposal to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee