

OUTCOME OF Juvenile Idiopathic Arthritis (JIA) Enthesitis related arthritis

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OUTCOME OF JUVENILE IDIOPATHIC ARTHRITIS - ENTHESITIS RELATED ARTHRITIS

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CERTIFICATE

This is to certify that this dissertation entitled “**Outcome of Juvenile idiopathic arthritis-enthesitis related arthritis**” presented here is the original work done by Dr.M.Saravanan, DM Postgraduate in the Department of Rheumatology, Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai-3 in partial fulfillment of the University rules and regulations for the award of D.M.Branch VII- Rheumatology, under my guidance and supervision during the academic period from 2008-2011.

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I solemnly declare that dissertation titled **“OUTCOME OF JUVENILE IDIOPATHIC ARTHRITIS – ENTHESITIS RELATED ARTHRITIS”** is done by me at the Department of Rheumatology, Madras Medical College& Rajiv Gandhi Government General Hospital, Chennai, during January 2009-March 2011 under the guidance and supervision of Prof.Dr.S.Rukmangatharajan M.D,D.M., FMMC.

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INTRODUCTION

AIM OF THE STUDY

REVIEW OF LITERATURE

MATERIALS AND METHODS

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DISCUSSION

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MASTER CHART

INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) is defined as arthritis in one or more joints persisting for 6 weeks or more, which begins before the 16th birthday and has no other known cause.

Enthesitis Related Arthritis (ERA) is a subtype that has replaced, but is not exactly overlapping with, previous definitions in children such as juvenile ankylosing spondylitis or syndrome of seronegative enthesitis arthritis.

ERA is defined as arthritis and enthesitis, or arthritis or enthesitis with at least two of the following: (1) sacroiliac joint tenderness, or inflammatory lumbosacral pain; (2) positive HLA-B27; (3) onset of arthritis in a boy 6 years old or older; (4) acute anterior symptomatic uveitis; or (5) history of ankylosing spondylitis, ERA, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative.

Exclusions include psoriasis in a first-degree relative, systemic features and a positive IgM RF on more than one occasion, 3 months apart. This form of JIA is more frequent in boys (male-to-female ratio of syndrome of seronegative enthesitis arthritis 7:1), although in some geographic areas it may be under recognized in symptomatic girls, who can have milder disease with less axial skeleton involvement. The onset

is typically in boys older than 6 years (commonly preteen or teenage) with peripheral arthritis affecting large joints, and there is a familial predilection. ERA is generally thought to be a form of spondyloarthropathy and has a strong association with HLA-B27. In patients who have the HLA-B27 gene, mechanisms may parallel those in adults with ankylosing spondylitis . There is overlap in terms of genetic factors and putative causative factors with reactive arthritis, although children with reactive arthritis are excluded from the ILAR criteria for JIA.

A typical feature of ERA is the presence of enthesitis (i.e., inflammation of the insertion site of tendons, ligaments, fascia and capsule into the periosteum of bone). The typical sites are the inferior pole of the patella, Achilles' tendon, and plantar fascia insertions into the calcaneus. Not all entheses are equally significant in ERA, and some are prone to mechanical damage in other pediatric conditions, such as in Osgood-Schlatter disease. Metatarsalgia is common in children and should not count as enthesitis. The arthritis of ERA typically affects the hips, knees or ankles and may be symmetric or asymmetric. Joints are painful and stiff, sometimes with night pain. At onset, spinal symptoms are rare, but in a subgroup of children with ERA progress to features more typical of adult ankylosing spondylitis with sacroiliac joint and spinal inflammation. This progression is more likely in boys, who are HLA-B27 positive and have spinal or sacroiliac joint pain within 1 year

of diagnosis. ERA is associated with an acute anterior uveitis, which typically presents as an acutely red, painful eye and needs immediate medical attention because if untreated it may lead to blindness.

In contrast to the western literature only 11-16% of patients with JIA have ERA, In India it is probably the commonest sub type of JIA seen clinically. Data on outcome of ERA patients from India are scarce. This study was taken up to assess the clinical profile and outcome of Juvenile idiopathic arthritis - enthesitis related arthritis.

REVIEW OF LITERATURE

Juvenile idiopathic arthritis (JIA) is an umbrella term for childhood arthritis of unknown cause.

JIA affects 1 in 1000 children.

Many of the subtypes of JIA have particular features, but some complications are common to several subtypes.

JIA is clearly distinct from adult rheumatoid arthritis.

Progress in the understanding of the genetics and pathogenesis of JIA has revealed subtype-specific associations and some common mechanisms of disease.

The principles of treating JIA are common to all subtypes because they involve a multidisciplinary approach, aiming to suppress inflammation early and maintain function.

It has been more than a century since Still eloquently described the differences between forms of childhood arthritis and adult rheumatoid arthritis. Despite many advances in understanding of genetic, pathologic and molecular influences on the disease, the cause or causes of juvenile arthritis are unknown and it remains a leading cause of acquired disability in childhood. In more recent years, juvenile idiopathic arthritis has become widely accepted as an umbrella term to

cover this heterogeneous group of conditions. The classification of JIA, proposed and subsequently revised by the International League of Associations for Rheumatology (ILAR), has now replaced previous nomenclature, including the European term, juvenile chronic arthritis, and the American term, juvenile rheumatoid arthritis^{1,2}.

JIA is defined as arthritis in one or more joints persisting for 6 weeks or more, which begins before the 16th birthday and has no other known cause. Each category has a list of possible inclusions and exclusions. A primary goal of such a system is to define mutually exclusive categories of idiopathic childhood arthritis based on predominant clinical and laboratory features, with the aim of improving therapy and management. Although the classification of JIA is based primarily on clinical features of the disease, with emphasis on presenting features, it is widely accepted that improved knowledge should lead to a more precise definition of the types of JIA, perhaps based on genetic, pathologic, or mechanistic information, and that such a classification would need to evolve or change, as understanding of the subtypes of juvenile arthritis and their pathophysiology improves. The increasing use of one system of classification would facilitate ready comparison of data and information from many studies and clinical trials.

Many of the types of childhood arthritis have distinct clinical features, and some of these features are rare in adult inflammatory arthritis. In JIA, in contrast to adult rheumatoid arthritis, large joints, such as the knees, wrists and ankles are typically more prominently involved than small joints. Subcutaneous nodules and rheumatoid factor (RF) seropositivity are unusual, but antinuclear antibody (ANA) seropositivity is frequent in some JIA subtypes. Some JIA subtypes have a majority onset in young childhood, although as yet there is no clear biologic explanation for why this is so. Examples include the systemic-onset and oligoarticular subtypes of JIA. In contrast, some JIA subtypes have an adult counterpart, such as psoriatic arthritis and RF-positive polyarticular JIA; these subtypes tend to have a slightly older onset in children. Some complications of JIA, such as osteoporosis or uveitis, can occur in many subtypes; others are more restricted to particular subtypes.

<i>ILAR Subtype</i>	<i>Peak Age of Onset (yr)</i>	<i>Female: Male; % of All JIA</i>	<i>Arthritis Pattern</i>	<i>Extra- articular Features</i>	<i>Investigation s</i>	<i>Notes on Therapy</i>
Systemic arthritis	2-4	1:1; 10% of JIA cases	Polyarticular, often knees, wrists, and ankles; also fingers, neck, and hips	Daily fever; evanescent rash; pericarditis ; pleuritis	Anemia; WBC ↑↑; ESR ↑↑; CRP ↑↑; ferritin ↑; platelets ↑↑ (normal or ↓ in MAS)	Less responsive to standard treatment with MTX and anti-TNF agents; consider IL-

<i>ILAR Subtype</i>	<i>Peak Age of Onset (yr)</i>	<i>Female: Male; % of All JIA</i>	<i>Arthritis Pattern</i>	<i>Extra-articular Features</i>	<i>Investigations</i>	<i>Notes on Therapy</i>
						1Ra in resistant cases
Oligoarthritis	<6	4:1; 50-60% of JIA (but ethnic variation)	Knees ++; ankles, fingers +	Uveitis in 30%	ANA positive in 60%; other tests usually normal; may have mildly ↑ ESR/CRP	NSAIDs and intra-articular steroids; occasionally require MTX
Polyarthritis, RF negative	6-7	3:1; 30% of JIA cases	Symmetric or asymmetric; small and large joints; cervical spine; TMJ	Uveitis in 10%	ANA positive in 40%; RF negative; ESR ↑ or ↑↑; CRP ↑/normal; mild anemia	Standard therapy with MTX and NSAIDs, then if nonresponsive, anti-TNF agents or other biologics
Polyarthritis, RF positive	9-12	9:1; <10% of JIA cases	Aggressive symmetric polyarthritis	Rheumatoid nodules in 10%; low-grade fever	RF positive; ESR ↑↑; CRP ↑/normal; mild anemia	Long-term remission unlikely; early aggressive therapy is warranted
Psoriatic arthritis	7-10	2:1; <10% of JIA cases	Asymmetric arthritis of small or medium sized joints	Uveitis in 10%; psoriasis in 50%	ANA positive in 50%; ESR ↑; CRP ↑/normal; mild anemia	NSAIDs and intra-articular steroids; second-line agents less commonly
Enthesitis-related arthritis	9-12	1:7; 10% of JIA cases	Predominantly lower limb joints affected; sometimes	Acute anterior uveitis; association with	80% HLA-B27+	NSAIDs and intra-articular steroids; consider sulfasalazine

<i>ILAR Subtype</i>	<i>Peak Age of Onset (yr)</i>	<i>Female: Male; % of All JIA</i>	<i>Arthritis Pattern</i>	<i>Extra-articular Features</i>	<i>Investigations</i>	<i>Notes on Therapy</i>
			axial skeleton (but less than adult AS)	reactive arthritis and IBD		as alternative to MTX

(ANA, antinuclear antibody; AS, ankylosing spondylitis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; ILAR, International League of Associations for Rheumatology; IL-1Ra, interleukin-1 receptor antagonist; MAS, macrophage activation syndrome; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; RF, rheumatoid factor; TMJ, temporomandibular joint; TNF, tumor necrosis factor; WBC, white blood cell count).

Long-term studies have shown that, as a whole, JIA is not as benign as previously thought, with rates of complete remission off medication still low in many subtypes, evidence for loss of quality of life in childhood, and 30% to 50% of patients experiencing ongoing inflammation or disability into adulthood. The imperative to investigate mechanisms of disease pathogenesis and search for new therapeutic avenues remains as strong as ever. A further drive to continue to aim for complete remission in JIA is the observation that when inflammation is

fully controlled, juvenile tissues, including synovium, cartilage, and bone, can undergo remarkable “healing” with restoration of function, in sharp contrast to adult arthritis.

EPIDEMIOLOGY

By definition, JIA begins before age 16 years. Young children 1 to 3 years old are most commonly affected, a pattern most noticeable in girls, in whom the disease is twice as common. Boys have a wider distribution of age at onset, with a small peak in incidence at 8 to 10 years. Systemic-onset JIA is an exception with a 1:1 female-to-male ratio. Studies of the incidence of childhood arthritis using either juvenile rheumatoid arthritis or juvenile chronic arthritis classifications have documented rates of 3.5 to 13.9 (confidence limits 9.9 to 18.8) per 100,000 children/yr in population-based cohorts, and a population-based study using ILAR JIA criteria suggested a rate of 15/100,000 children/yr.^{7,8} Prevalence of chronic arthritis in childhood has been estimated as 148/100,000 children in a Norwegian study, and 400/100,000 children in a survey of 12-year-old schoolchildren.¹¹ In the latter study, all children were examined by a pediatric rheumatologist, which may explain the higher prevalence estimate. Most quoted studies are from populations of northern European descent, but some reports suggest arthritis may be less common in Japanese, black and Asian children.¹³

GENETICS

Despite significant advances in genetics and molecular immunology, understanding of the etiology of JIA is piecemeal. Genetic factors and environmental triggers are thought to play a part ultimately leading to abnormalities in the cellular, humoral, and innate arms of the immune system.^{18,19,20} The evidence for a genetic contribution to JIA comes from several sources. Twin studies show a high concordance of disease in monozygotic twins. A study of 164 affected sibling pairs with JIA showed a 70% concordance for gender, 73% for disease onset, and 66% for disease course, considerably higher than in a non-affected sibling pair cohort. First-degree relatives of children with JIA have a higher rate of autoimmune disease than controls. Genetic influences on JIA susceptibility and phenotype are polygenic, and a more recent genome-wide scan in JIA affected sibling pair families has supported the idea that multiple genetic loci contribute to JIA susceptibility.

The strong associations of specific alleles with JIA are within the major histocompatibility complex (MHC) system and were the first to be documented. Among the MHC class I loci, HLA-B27 is strongly associated with spondyloarthropathy, which in children is now termed enthesitis-related arthritis (ERA), whereas HLA-A*0201 is increased in oligoarthritis.^{21,22,23} Multiple studies have revealed an increase in HLA-DR alleles, of which the strongest are DRB1*0801 and DRB1*1101

with oligoarticular JIA and DRB1*1301, in particular in ANA-positive cases.²³ Several haplotypes across the MHC confer an increased risk for all types of JIA, such as DRB1*08-DQA1*0401-DQB1*0402, which confers an odds ratio of 6.1 for persistent oligoarticular JIA and 10.3 for extended oligoarticular JIA. Frequency of the DRB1*1301-DQA1*01-DQB1*06 haplotype distinguishes persistent from extended oligoarticular JIA, whereas DRB1*0801 and DRB1*1401 are associated with polyarticular JIA.

Together these effects may be large; in one study, the presence of the combination of the HLA-DRB1*0801, HLA-DRB1*1101, and HLA-DPB1*0201 alleles conferred a relative risk. Some associations closely mirror the associations of the corresponding adult disease, such as the strong association of the HLA-B27 allele with ERA and the HLA-DRB1*0401 with RF-positive polyarticular JIA. Some of these allele/subtype associations show an age-specific effect, in that they confer risk over a specific age range only. Although systemic JIA shows weaker associations with HLA alleles, even in this subtype, specific haplotypes (e.g., DRB1*11-DQA1*05-DQB1*03) are increased compared with control subjects.

Inflammatory cytokines have been an important target for drug development in JIA, and similarly their gene polymorphisms have been a key area of scrutiny. Several HLA-independent tumor necrosis factor (TNF) haplotypes are significantly associated with JIA, but the functional consequences of these alleles are unclear. Some of the best characterized non-HLA genetic associations in JIA have been established in systemic JIA. The hypothesis suggesting a link between systemic JIA and interleukin (IL)-6 was proposed in 1993, with many of the clinical features in systemic JIA resembling the phenotype of IL-6 overexpression (e.g., fevers, stunted growth, anemia). A polymorphism (-174G/C) in the regulatory region of the IL-6 gene alters transcription of IL-6 in response to IL-1 and lipopolysaccharide; patients with systemic JIA have significantly lower frequency of the protective CC genotype, and the IL-6 -174G allele was confirmed as a susceptibility gene for systemic JIA.

More recent haplotype analysis of the IL-6 gene has confirmed a haplotype association with systemic JIA. A polymorphism in the promoter region of the macrophage inhibitory factor (MIF) gene is associated with JIA. This polymorphism (MIF -173*C) results in higher MIF production in the serum and synovium of JIA patients and has been shown to be predictive of outcome of intra-articular steroid injections in systemic JIA.

The anti-inflammatory gene IL-10 was first studied in oligoarticular JIA. The “ATA” haplotype of three single nucleotide polymorphisms at the 5′ flanking end of the gene is associated with lower production of IL-10 by peripheral blood mononuclear cells, and was found more frequently in the more severe subtype of JIA, extended oligoarticular JIA, than the milder persistent oligoarticular JIA. IL-10 and its family member IL-20 were found to be associated with systemic JIA. The gene PTPN22, a negative regulator of T cell responses, has been suggested to be associated with JIA also, but current evidence is conflicting.^{24,25} In contrast to studies using the candidate gene approach, future novel genetic associations will be elucidated through whole-genome scanning, requiring large multicenter case-control cohorts.

ENVIRONMENT

A study of socioeconomic factors in the etiology of JIA suggested that high parental income and being an only child may be associated with a higher risk of disease, and in a Finnish study of more than 58,000 births, fetal exposure to smoking has been suggested to increase the risk of JIA in girls. The evidence that genetic risk alleles, such as those associated with HLA antigens, confer different risk of JIA across different ages, strongly suggests that crucial environmental triggers, which change with age, may be involved in the initiation of JIA.

Microbial triggers for JIA remain elusive. *Borrelia burgdoferi*, the infectious agent responsible for Lyme disease, *Mycoplasma pneumoniae*, and several viruses, such as rubella and parvovirus, can cause a clinical picture similar to JIA, leading to the hypothesis that JIA represents an immunologic response to an infectious trigger. Bacterial or viral DNA can be isolated from the joints or serum of JIA patients, but no single agent has been identified as a cause of JIA, and in most cases of JIA no persisting infectious agent can be shown.²⁸ Epidemiologic studies searching for infectious “outbreaks” or seasonal variation in incident JIA cases, or in pregnant mothers whose children subsequently develop JIA, have provided conflicting results.

An alternative role for microbial pathogens in the pathogenesis of JIA has been suggested through molecular mimicry. Heat shock proteins are proteins expressed by microbial and human cells in response to stress. Bacterial heat shock proteins are strong immunogens and may generate cross-reactive immune responses to self-heat shock proteins in humans. In oligoarticular JIA, reactivity to self-heat shock proteins correlates with disease remission, and synovial T cells generate a regulatory cell phenotype in response to self-heat shock protein 60, which was not detectable in the more severe polyarthritis subgroup.

PATHOGENESIS

The pathologic hallmark of juvenile inflammatory arthritis is the inflamed synovium. Histology of this tissue shows thickened synovium that is highly vascular and shows marked hyperplasia of synoviocytes in the lining layer and a dense infiltrate of inflammatory cells, comprising T cells, macrophages and in some cases B cells and natural killer cells.^{31,32} The hypertrophied synovial layer is highly vascular, with endothelium expressing markers of activation such as HLA-DR and intracellular adhesion molecule 1. The vascularity is likely related to the increased production of proangiogenic factors, such as vascular endothelial growth factor and the angiogenic chemokines.

Recruitment of this inflammatory infiltrate is likely mediated by multiple chemokines shown to be increased in JIA, including CCL3, CCL5, and CXCL10; IL-8; and monocyte chemotactic protein-1.^{37,38}

The strong association of many JIA subtypes with genetic variants at HLA loci, the central role of HLA class I and II proteins in T cell function, and the predominance of T cells in pathologic JIA synovial tissue and fluid led to intense investigation of the role of T cells in the pathology of JIA. T cells within the JIA joint are highly activated memory cells, expressing rapidly upregulated (CD69) and persistent (DR) activation markers. These T cells express a restricted set of T cell receptors: The clonotypes are large and long-lived, and the same

hierarchy of clones re-expands during a relapse or flare of disease. The finding that this oligoclonality in the intra-articular T cell population is more marked in CD4⁺ T cells in oligoarthritis (which is associated with class II HLA-DR genes), and yet more marked in CD8⁺ T cells in ERA (which is associated with the class I allele HLA-B27), supports the concept that recognition of MHC-peptide complexes by T cells plays a role in the pathogenesis of JIA.

Early work on inflammatory cytokines produced by synovial T cells suggested that these were heavily skewed toward a T helper type 1 (Th1) CCR5+CXCR3⁺ interferon- γ -producing lineage.⁴⁶ More recent evidence suggests, however, that another proinflammatory T cell cytokine, IL-17, produced by Th17 cells, has an important role in JIA. Th17 cells are enriched in the joint in JIA, and their numbers are higher in children with the more severe extended oligoarticular JIA compared with children with milder, persistent oligoarticular disease.

Many inflammatory cytokines and chemokines are abnormally increased in JIA and found at the site of destructive synovitis. Subtype differences have emerged, which may allow a “subtype-specific” profiling of serum or synovial fluid in the future, although such measurements have to take into account circadian rhythms and the short half-lives of these mediators. Systemic JIA is associated with high levels of TNF α , IL-1, IL-6, MIF, and IL-18.⁵⁰ In cases of classic

systemic JIA, the levels of IL-6 and IL-1 receptor antagonist increase and decrease in parallel with the fever and rash. IL-6 and MIF levels are each associated with disease activity in systemic JIA, and high synovial MIF levels predict poor response to intra-articular steroid injection. IL-1 has been suggested to have a major role in the pathogenesis of systemic JIA, although results in this field are conflicting.

In addition to the proinflammatory, destructive process within the joint, there is strong evidence for ongoing immunoregulation in JIA. The existence of a mild form of arthritis in which full-blown immunopathology can resolve and disease can enter full remission (known as persistent oligoarticular JIA) provides a unique model in autoimmunity: a mild self-remitting autoimmune pathology, which can be compared with more severe clinical subtypes. Children with persistent oligoarticular JIA have evidence of immunoregulation as shown by high numbers of CD25⁺ foxp3⁺ regulatory T cells in the joint, and these cells correlate with clinical phenotype and outcome. In addition, T cells specific for the conserved self-antigen heat shock proteins have been shown to be present at significantly higher numbers in children destined to have a mild disease course, and these self-antigen heat shock protein-specific cells are thought to play a regulatory role. The crucial role of dendritic cells in the control of this immunoregulation of JIA is a field of intense investigation.⁵⁴

In addition to cells of the adaptive immune system, many other parts of the immune system are abnormally activated in JIA, including synovial macrophages, dendritic cells, and neutrophils.⁵⁵ Modern high-methods of gene expression profiling and proteomics have shown differences between JIA clinical subtypes in several cell populations and between JIA patients before and after treatment and compared with controls. Ultimately, the understanding of pathologic mechanisms and alterations in the balance between immune activation and regulation, during disease and in response to treatment, should lead to a new set of molecular tools with which to separate clinical subtypes, predict disease course, and select tailored therapies for every child more accurately.

CLINICAL FEATURES OF SUBTYPES OF JUVENILE IDIOPATHIC ARTHRITIS

SYSTEMIC ARTHRITIS

Systemic JIA is defined as arthritis associated with systemic features, typically quotidian spiking fevers of 39°C or greater for more than 2 weeks, accompanied by at least any one of the following: an evanescent rash, lymphadenopathy, serositis, or hepatosplenomegaly. This clinical subtype was previously known as Still's disease and has a recognized adult-equivalent condition, adult-onset Still's disease. Systemic JIA occurs in young children with a peak age in most series of 2 to 4 years. The incidence is the same in both sexes in whites, in contrast to the other types of JIA. The prevalence of systemic JIA

approximates to 10 cases per 100,000, representing about 10% of JIA as a whole, although some surveys have suggested that it may be more frequent in Japan and India.

There is only a weak association between the HLA region and systemic JIA in whites, but there is good evidence that genetic predisposition constitutes at least part of the cause of systemic JIA. Non-HLA genes, such as those coding for macrophage MIF, have been shown to be associated with JIA as a whole, and a variant of the IL-6 gene confers susceptibility. These genes are thought to predispose the patient to a vigorous inflammatory response to stimuli, such as infectious agents, and the net effect of the interaction between proinflammatory and anti-inflammatory proteins is probably the key to the clinical features in this subtype of JIA. IL-6 and IL-1 may play a role in the pathogenesis of systemic JIA and have been proposed as therapeutic targets. Several monocyte-derived and neutrophil-derived proinflammatory factors also are abnormal in systemic JIA, including the myeloid-related proteins S100A8 and S100A9, and neutrophil-derived S100A12. Abnormalities of the adaptive immune system in systemic JIA may include a defect in perforin. Low levels are associated with severe disease, but can reverse when disease is controlled.

Clinical Manifestations

The fever is typically spiking in character with a peak of at least 39°C. It occurs once or twice a day and recurs each day (quotidian). This quotidian fever is accompanied by an evanescent salmon pink macular/urticarial rash, which can be itchy. The child is usually unwell and irritable during the fever, but often recovers in between. Other accompanying symptoms are headaches (sometimes with signs of meningism), arthralgia or arthritis, myalgia, abdominal pains from serositis that can mimic an acute abdomen, breathlessness and chest pains on lying flat indicating pericarditis, and acute chest pains from pleuritis. The severity of symptoms varies widely, ranging from fever and rash for 2 to 3 weeks followed by mild arthritis, to simultaneous onset of all the above-described symptoms. In the most severe cases, children also may present with features of secondary hemophagocytic lymphohistiocytosis (also known as macrophage activation syndrome), with signs of anemia, jaundice, and purpura in later stages.

Laboratory Features

There are no specific tests for systemic JIA, but there are characteristic patterns of laboratory abnormalities. There is typically a very high C-reactive protein and erythrocyte sedimentation rate, leukocytosis with neutrophilia, thrombocytosis and anemia, which may be profound. Liver enzymes, ferritin, and coagulation screen may be

abnormal in severe cases, and polyclonal hypergammaglobulinemia is frequent. There are no specific autoantibodies.

OLIGOARTHRITIS

Oligoarticular arthritis is the most common form of JIA and preferentially affects girls (female-to-male ratio of 4:1), with a peak onset before 6 years of age. It affects about 60 per 100,000 white children, but rates vary in different ethnic groups. Oligoarticular JIA affects four or fewer joints in the first 6 months of disease. If more than four joints become involved after 6 months, it is defined as extended oligoarthritis; otherwise, it is known as persistent oligoarthritis. There are several exclusion factors including psoriasis in the patient or a first-degree relative, systemic features, a positive IgM RF on more than one occasion 3 months apart, or a positive HLA-B27 test when in a boy in whom arthritis starts at 6 years or older.

Clinical Manifestations

Children with oligoarthritis present with involvement of one to four joints, most commonly the knees and ankles. Small joints of the hands are the third most commonly affected, but this pattern may portend the later onset of psoriatic arthritis. Temporomandibular joint arthritis is common, but is often detected late in the course of the disease because symptoms are uncommon. Initial wrist involvement is rare and may indicate progression to extended oligoarthritis, or

polyarticular disease. Shoulders are rarely involved. Cervical spine disease may be manifest by torticollis. Most children complain of pain, morning stiffness, and gelling, and a parent may notice a limp and joint swelling, or in a young child, a reluctance to walk and return to crawling. Twenty-five percent of cases seem to be painless, however, and only swelling is observed.

The most common extra-articular manifestation is iridocyclitis, also known as chronic anterior uveitis. Twenty percent to 30% of children with oligoarticular JIA develop uveitis, which is generally asymptomatic. The eye is neither red nor photophobic. Uveitis is more prevalent in children who are ANA positive.^{62,63} All children with oligoarticular JIA should have a mandatory slit lamp examination of the eyes to rule out uveitis by an experienced ophthalmologist at presentation and every 3 to 4 months for the first year and then for several years, with recommended screening times depending on age at onset. Some physicians decrease the surveillance to every 6 months if the ANA is negative because a positive ANA test is a predictor of uveitis.⁶⁴

Laboratory Features

Of children with oligoarthritis, 50% to 70% have a positive ANA test, typically 1:40 to 1:320 depending on the test system, and the rate is even higher in girls with an early onset. In some cases, a child has

mildly or moderately elevated acute-phase reactants, such as erythrocyte sedimentation rate or C-reactive protein, and in a few cases a mild anemia is present. A high erythrocyte sedimentation rate may predict progression to the extended subtype. Elevated acute-phase reactants may suggest other conditions, such as subclinical inflammatory bowel disease with associated arthropathy.

POLYARTHRITIS, RHEUMATOID FACTOR NEGATIVE

RF-negative polyarthritis is defined as arthritis affecting five or more joints in the first 6 months of disease, with a negative RF test. Patients who meet the criteria for systemic arthritis, ERA, and psoriatic arthritis are excluded. Extended oligoarthritis, another subgroup with a polyarticular course, is distinguished from RF-negative polyarthritis by having five or more affected joints after only 6 months of disease. There is a risk of misclassifying these two groups if a patient's presentation is delayed, or progression of arthritis occurs around the time point of 6 months.

RF-negative polyarthritis constitutes 20% to 30% of new cases. The British Paediatric Rheumatology National Diagnostic Register of 311 patients recorded a mean age of onset of 6.5 years for this subtype, with girls outnumbering boys by 3:1. Age-related analysis reveals a bimodal distribution of onset, however, with one peak around 3.5 years and the other around 10 to 11 years.

Arthritis is usually insidious and can be symmetric or asymmetric, affecting large and small joints. The cervical spine and temporomandibular joint are often involved. Some authors distinguish two clinical subgroups on the basis of ANA: (1) an ANA-positive group consisting of young girls (<6 years old) with an asymmetric-onset arthritis and at a high risk of uveitis, and (2) a slightly older group (7 to 9 years old) of ANA-negative patients having symmetric involvement of large and small joints. Uveitis occurs in 5% to 20% of patients in the RF-negative polyarthritis JIA subtype, generally patients with few affected joints.

Laboratory Features

Polyarthritis may be associated with elevated acute-phase reactants and mild anemia. The ANA test is positive in 40%, and the RF is negative by definition.

POLYARTHRITIS, RHEUMATOID FACTOR POSITIVE

RF-positive polyarticular JIA is defined as arthritis affecting five or more joints in the first 6 months of disease and a positive RF test on two occasions at least 3 months apart. RF-positive polyarthritis constitutes 5% to 10% of cases under the juvenile rheumatoid arthritis or juvenile chronic arthritis classifications. In the JIA classification, RF testing is crucial to avoid large numbers of children with polyarthritis being unclassifiable. RF-positive polyarthritis is more common in girls,

with reported female-to-male ratios of 5.7 to 12.8, and can be considered as part of the spectrum of rheumatoid arthritis, sharing immunogenetic and serologic factors. HLA-DRB1*0401 is strongly associated, and the HLA-DRB1*0401 DQA1*03 DQB1*03 haplotype carries an increased odds ratio of 3.9 for this subtype, yet is protective for other subtypes of JIA. Anti-cyclic citrullinated peptide antibodies have been reported in 57% to 73% of this JIA subtype. Disease expression differs from adults, perhaps because of the effects of environmental factors, the effects of arthritis on a growing body, and the psychosocial impact of chronic disease during adolescence, which is itself a period of significant change in an individual's independence and self-identity.

Clinical Manifestations

The arthritis is typically an aggressive, symmetric polyarthritis affecting the small joints of the hands, typically the proximal interphalangeal joints, metacarpophalangeal joints and wrists and with a large joint involvement in a pattern that resembles rheumatoid arthritis. Children frequently have more than 30 joints with arthritis. At onset, low-grade fever may be present, but it is distinctly different from systemic JIA. Felty's syndrome (splenomegaly and leukopenia) can occur in childhood RF-positive polyarthritis. Rheumatoid nodules occur in 10% of cases, most frequently around the elbow. Other extra-articular

manifestations are reported less often than in adults. Uveitis is an unusual feature of this subtype.

Laboratory Features

Polyarthritis may be associated with elevated acute-phase reactants and anemia (normocytic, normochromic). The ANA test is positive in a few cases, and the RF is by definition positive on two occasions 3 months apart. Similar to adult rheumatoid arthritis, RF testing typically detects IgM-anti-IgG. In these patients, anti-cyclic citrullinated peptide antibodies may be more specific and as in adults are associated with erosive arthritis.

JIA- PSORIATIC ARTHRITIS

It is defined as the combination of arthritis and psoriasis, or arthritis and at least two of the following: dactylitis, nail abnormalities (two or more nail pits, or onycholysis), or family history of psoriasis in a first-degree relative. The earlier proposed ILAR classification[[] included second-degree relatives with psoriasis, but this was believed to classify too many cases incorrectly. A full family history is crucial, and without this children may be misclassified.

Psoriatic JIA represents 2% to 15% of all JIA. In the United States, it is more common in whites than other racial groups; approximately 90% of patients are white. Girls are slightly more affected than boys, and the typical age of onset is 7 to 10 years, with

psoriasis typically occurring within 2 years of the onset of arthritis, although it can follow arthritis by many years. The specific etiology is unknown, but there is a strong genetic component with 40% of patients with psoriasis having an affected relative, and several candidate HLA and non-HLA genes have been identified. More recent data from adults have implicated the newly identified IL-17-secreting T cells (Th17) and related cytokine IL-22 in the pathogenesis of psoriasis.

Clinical Manifestations

Arthritis is typically asymmetric and can involve large joints (commonly knees and ankles) and small joints, classically dactylitis, more commonly in the feet than in the hands, and distal interphalangeal joints. The total number of joints generally is limited, and children frequently follow an oligoarticular course. Psoriatic JIA is associated with uveitis in 15% of children. These features are typical of oligoarthritis, and many children are first classified as having oligoarticular JIA before psoriasis is manifest in the child or relative. A more recent study of childhood psoriatic arthritis argued for two distinct subpopulations. The older group, median age 9.5 years were more likely to have oligoarthritis and had higher remission rates. Although many adults with psoriatic arthritis have features of a spondyloarthropathy, such as sacroiliitis or enthesitis, in the JIA classification these children are classified as having ERA, or, if they have psoriasis, are unclassified.

Laboratory Features

Children with psoriatic arthritis may have mild elevation of the erythrocyte sedimentation rate, C-reactive protein, and platelets, and a mild anemia of chronic disease. The ANA test is positive in half of children with psoriatic arthritis. RF is negative by definition.

UNCLASSIFIED JUVENILE IDIOPATHIC ARTHRITIS

Because of the exclusion criteria within the ILAR classification, strict adherence to the ILAR system leads to some children being defined as unclassifiable ; this is distinct from the previous European League Against Rheumatism or American College of Rheumatology criteria for juvenile arthritis, which did not include an unclassified group. The unclassified cases are patients who are defined as not having fulfilled sufficient inclusion criteria for any category or are excluded by fulfilling criteria for more than one category. A child in the oligoarthritis subgroup would be excluded if he or she had a family history of psoriasis in a first-degree relative. Although this system caused considerable controversy when proposed, it is based on the premise that classification is primarily a research tool, and so the provision of an undifferentiated category would offer greater homogeneity for the remaining subgroups.

For clinical purposes, treatment of such children follows the same guidelines as outlined earlier. Ultimately, the system for classifying JIA

reflects current understanding of the disease's pathophysiology. As this knowledge improves, future revisions would be increasingly useful in a clinical setting because patient categorization would offer accurate predictions of clinical response and prognosis.

REVIEW OF ENTHESTITIS-RELATED ARTHRITIS

ERA is a subtype that has replaced, but is not exactly overlapping with, previous definitions in children such as juvenile ankylosing spondylitis or syndrome of seronegative enthesitis arthritis. ERA is defined as arthritis and enthesitis, or arthritis or enthesitis with at least two of the following: (1) sacroiliac joint tenderness, or inflammatory lumbosacral pain; (2) positive HLA-B27; (3) onset of arthritis in a boy 6 years old or older; (4) acute anterior symptomatic uveitis; or (5) history of ankylosing spondylitis, ERA, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative. Exclusions include psoriasis in a first-degree relative, systemic features and a positive IgM RF on more than one occasion 3 months apart.

This form of JIA is more frequent in boys (male-to-female ratio of syndrome of seronegative enthesitis arthritis 7:1), although in some geographic areas it may be underrecognized in symptomatic girls, who can have milder disease with less axial skeleton involvement. The onset is typically in boys older than 6 years (commonly preteen or teenage) with peripheral arthritis affecting large joints, and there is a familial predilection. ERA is generally thought to be a form of spondyloarthropathy and has a strong association with HLA-B27. In patients who have the HLA-B27 gene, mechanisms may parallel those in

adults with ankylosing spondylitis . There is overlap in terms of genetic factors and putative causative factors with reactive arthritis, although children with reactive arthritis are excluded from the ILAR criteria for JIA.

CLINICAL MANIFESTATIONS

A typical feature of ERA is the presence of enthesitis. The typical sites are the inferior pole of the patella, Achilles' tendon, and plantar fascia insertions into the calcaneus. Not all entheses are equally significant in ERA, and some are prone to mechanical damage in other pediatric conditions, such as in Osgood-Schlatter disease. Metatarsalgia is common in children and should not count as enthesitis. The arthritis of ERA typically affects the hips, knees, or ankles, and may be symmetric or asymmetric. Joints are painful and stiff, sometimes with night pain. At onset, spinal symptoms are rare, but in a subgroup of children with ERA progress to features more typical of adult ankylosing spondylitis with sacroiliac joint and spinal inflammation. This progression is more likely in boys, who are HLA-B27 positive and have spinal or sacroiliac joint pain within 1 year of diagnosis. ERA is associated with an acute anterior uveitis, which typically presents as an acutely red, painful eye and needs immediate medical attention because if untreated it may lead to blindness .

LABORATORY FEATURES

There is no diagnostic laboratory test, although HLA-B27 is present in 80% to 90% of cases and helps establish this diagnosis. The erythrocyte sedimentation rate may be mildly or markedly increased, and there may be a mild anemia, but these also should raise the suspicion that the patient may have subclinical inflammatory bowel disease. RF is negative by definition; ANA may be positive.⁶⁴ Ultrasound can distinguish enthesitis even in asymptomatic individuals.

HUMAN LEUKOCYTE ANTIGEN (HLA) B27

It is a class I surface antigen encoded by the B locus in the major histocompatibility complex (MHC) on chromosome 6 and presents antigenic peptides (derived from self and non-self antigens) to T-cells. HLA-B27 is strongly associated with ankylosing spondylitis (AS), and other associated inflammatory diseases referred to collectively as "spondyloarthritis". The prevalence of HLA-B27 varies markedly in the general population. For example, about 8% Caucasian, 4% North Africans, 2-9% Chinese, and 0.1-0.5% Japanese possess this gene. In Northern Scandinavia (Lapland), 24% of people are HLA-B27 positive, while 1.8% have associated ankylosing spondylitis (AS). Examining HLA types.

SEROTYPE AND ALLELE NAMES

There are two parallel systems of nomenclature that are applied to HLA. The, first, and oldest system is based on serological (antibody

based) recognition. In this system antigens were eventually assigned letters and numbers (e.g. HLA-B27 or, shortened, B27). A parallel system was developed that allowed more refined definition of alleles, in this system a "HLA" is used in conjunction with a letter * and four or more digit number (e.g. HLA-B*0801, A*68011, A*240201N N=Null) to designate a specific allele at a given HLA locus. HLA loci can be further classified into MHC class I and MHC class II (or rarely, D locus). Every two years a nomenclature is put forth to aid researchers in interpreting serotypes to alleles.

SEROTYPING

In order to create a typing reagent, blood from animals or humans would be taken, the blood cells allowed to separate from the serum, and the serum diluted to its optimal sensitivity and used to type cells from other individuals or animals. Thus serotyping became a way of crudely identifying HLA receptors and receptor isoforms. Over the years serotyping antibodies became more refined as techniques for increasing sensitivity improved and new serotyping antibodies continue to appear. One of the goals of serotype analysis is to fill gaps in the analysis. It is possible to predict based on 'square root' 'maximum-likelihood' method, or analysis of familial haplotypes to account for adequately typed alleles. These studies using serotyping techniques frequently revealed, particularly for non-European or north East Asian populations a large number of null or blank serotypes. This was particularly problematic for

the Cw locus until recently, and almost half of the Cw serotypes went untyped in the 1991 survey of the human population.

There are several types of serotypes. A broad antigen serotype is a crude measure of identity of cells. For example HLA A9 serotype recognizes cells of A23 and A24 bearing individuals, it may also recognize cells that A23 and A24 miss because of small variations. A23 and A24 are split antigens, but antibodies specific to either are typically used more often than antibodies to broad antigens.

DIFFERENTIAL DIAGNOSIS

Some children with prolonged reactive arthritis, or arthritis associated with inflammatory bowel disease, have enthesitis and would be classified as having ERA if the infective agent were not identified, or until inflammatory bowel disease is diagnosed. Other conditions that may mimic ERA include reactive arthritis in children and pain syndromes; children with widespread amplified musculoskeletal pain may have very tender entheses that can be mistaken for enthesitis.

TREATMENT

Treatment of ERA is similar to that for oligoarthritis and polyarthritis.^{66,67} Most patients respond to intra-articular corticosteroid injections, but many need a disease-modifying antirheumatic drug and respond well to sulfasalazine or methotrexate, although there has been no comparison of the two agents in children.^{68,69} If disease is severe, a

course of intravenous pulse methylprednisolone is often helpful. Children with enthesitis require an NSAID for symptomatic relief. Many physicians empirically favor certain NSAIDs for enthesitis, specifically diclofenac and indomethacin. Occasionally, corticosteroid injection of the plantar fascial insertion on the calcaneus is helpful. Physical therapy is central to management (as for all JIA), and orthotics and shoe modification can help greatly. These measures have not proved to modify the course of disease significantly, in particular, axial and spinal inflammation.

In open label studies, the anti-TNF- α agents infliximab and etanercept have been shown to be effective agents for axial disease.^{73,74} Anti-TNF- α agents should be used early in the course of axial disease, before irreversible damage from spinal erosion and fusion occurs. Anti-TNF- α agents also are associated with improvement in peripheral arthritis and enthesitis.

The modern treatment of JIA involves a range of specialists. Early use of combination of disease-modifying agents can suppress disease activity in many cases. Pediatric rheumatologists have in their favor the remarkable capacity for childhood growth and development to allow repair and restoration of function, in contrast to adults with inflammatory arthritis.

A persistent block to good outcome in many areas of the world is a delay in recognition, late referral and diagnosis of JIA.

When JIA is recognized, children who receive active treatment through a multidisciplinary approach should have an improving prognosis in the years to come. The advent of new biologic therapies and rapid translation of basic research into therapeutic strategies and an increased willingness on the part of regulatory bodies to make new therapies available to children should combine to continue to improve the outlook for children with arthritis.

Thus the long-term outcome of ERA is unknown, but a proportion of these children progress to the adult form of ankylosing spondylitis. Enthesitis can be more symptomatic in teens and young adults and improves with age. Spinal and sacroiliac joint involvement in teenagers, if left untreated, can lead to ankylosis, as in adults. Boys with HLA-B27 and hip arthritis are at higher risk of developing progressive spinal involvement.

AIM

The aim of the study is

- 1) To study the clinical profile and outcome of Juvenile idiopathic arthritis -enthesitis related arthritis.
- 2) To study the incidence of Juvenile ankylosing spondylitis.
- 3) To study the association of HLA_B27 and sacro iliac joint involvement.

MATERIALS AND METHODS

The study period was from January 2009 to March 2011. History, clinical examination, radiological imaging like musculoskeletal X-rays, musculoskeletal USG and CT of sacroiliac joints, biochemical investigations and immunological investigations were done for all patients.

Material and Selection: Inpatients and outpatients of Department of Rheumatology, Rajiv Gandhi Govt. General Hospital and Madras Medical College, Chennai. The study was under taken after obtaining approval from the institutional ethical committee. An informed consent was obtained from all patients and parents.

The study period was from January 2009 to March 2011.

Sample size: 50

Study design: Cross sectional study

Inclusion criteria are [1]: onset of arthritis before the 16th birthday and persisting for at least 6 weeks; arthritis and enthesitis, or arthritis or enthesitis with at least 2 of

- a) Presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain,
- b) Presence of HLA-B27 antigen,

- c) Onset of arthritis in a male over 6 years of age.
- d) Acute (symptomatic) anterior uveitis
- e) History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative.

By definition, patients with psoriasis or a history of psoriasis in the patient or first-degree relative, presence of IgM rheumatoid factor and systemic JIA are not included in ERA subtype.

JADI (Juvenile articular damage index) scores were calculated as described previously. The index is composed of articular (JADI-A) and extraarticular (JADI-E) damage. In the JADI-A, 36 joints or joint groups are assessed for the presence of damage: cervical spine, shoulders, elbows, wrists, individual metacarpophalangeal and proximal interphalangeal joints, hips, and knees; right and left temporomandibular joints, ankle and subtalar joints and metatarsophalangeal joint of each foot are considered as a single unit. The damage observed in each joint is scored as 1 in case of partial damage, or 2 in case of severe damage, ankylosis, or prosthesis. Contractures and other joint deformities are scored when they are completely explained by prior damage and are not due to active arthritis and are present for at least 6 months. For each joint, only the most severe lesions are scored. The maximum possible JADI-A score is 72.

For JADI-E, muscle atrophy, osteoporosis with fractures or vertebral collapse, avascular necrosis of bone, significant abnormality of the vertebral curve due to leg length discrepancy or hip contracture, significant leg length discrepancy or growth abnormality of a bone segment, striae rubrae, subcutaneous atrophy resulting from intraarticular corticosteroid injection, growth failure, pubertal delay, diabetes mellitus and amyloidosis are scored as 1 if present; ocular complications like cataract or other complications of uveitis were scored as 1 if present, 2 if surgery was required and 3 in case of blindness.

Abdominal fat pad analysis for amyloidosis was done if there was edema, hypertension, anasarca, proteinuria or disproportionately increased ESR. Growth was assessed by plotting height and weight on standardized Indian pediatric growth charts. Growth failure was defined as the presence of two or more of the following: less than 3rd percentile height for age, growth velocity less than 3rd percentile for age or crossing at least 2 percentile on growth chart. Delayed puberty was defined if no testicular enlargement occurred by 14 years of age.

Educational level achieved, loss of school years, functional status measured by HAQ-S were also recorded. For the purposes of analysis, the HAQ-S score was divided into 4 categories: 0 = no disability, >0 and ≤ 0.5 = mild disability, >0.5 and ≤ 1.5 = moderate disability, and > 1.5 =

severe disability . Hundred mm Visual Analogue Scale (VAS) was used for parent/patient's assessment of their disease.

Examination included physician's global assessment on 100 mm VAS, number of active joints as defined by presence of swelling (excluding bony swelling) or any two of limitation of motion (LOM), pain, heat, or tenderness and number of joints with limited range of motion (ROM); 67 joints were assessed .

Enthesitis was defined as discretely localized tenderness at the point of insertion of ligaments, tendons, joint capsules, or fascia to bone. Anterior lumbar flexion was assessed using the modified Schober's method. Reduced lumbar flexion was defined as values ≤ 6.5 cm in boys and ≤ 5.5 cm in girls. Inflammatory back pain was defined as lumbosacral spinal pain at rest, with morning stiffness that improved with movement. Erythrocyte Sedimentation rate (ESR) was measured by Westergren method.

ENTHESITIS

Enthesitis is inflammation of the entheses, the sites where tendons or ligaments insert into the bone. It is also called enthesopathy or any pathologic condition involving the entheses. The entheses are any point of attachment of skeletal muscles to the bone, where recurring stress or inflammatory autoimmune disease can cause inflammation or occasionally fibrosis and calcification. One of the primary entheses

involved in inflammatory autoimmune disease is at the heel, particularly the Achilles tendon.

It is associated with HLA B27 arthropathies like ankylosing spondylitis, psoriatic arthritis, and reactive arthritis (Reiter's syndrome).

Symptoms include multiple points of tenderness at the heel, tibial tuberosity, iliac crest, and other tendon insertion sites. The entheses of the lower limbs are more frequently involved than those of the upper limbs, and heel enthesitis is the most frequent. Enthesal pain may be mild or moderate as well as severe and disabling. Peripheral enthesitis may be observed in all forms of spondyloarthritis, including the undifferentiated forms, and may, for a prolonged period, be the only longstanding clinical manifestation of the B27-associated disease process. The conceptual understanding of spondyloarthritis and the ability to image sites of skeletal inflammation accurately, i.e. ultrasound and magnetic resonance imaging, confirm that enthesitis is the primary lesion of spondyloarthritis. This advance has been occurring simultaneously with the therapeutic advances in spondyloarthritis due to the introduction of anti-tumour necrosis factor-alpha agents.

Patients with features of enthesitis were subjected to under gone Musculoskeletal Ultra Sound of affected entheses. Ultrasound was done by a radiologist who was trained in musculoskeletal imaging. The frequency of Ultra Sound probe was 10.5 MHz.

X RAY SACROILIAC JOINT

Conventional x-ray still remains as the imaging method most utilized in the clinical practice. An international consensus still remains to be reached regarding the best technique and view for radiographic evaluation of the sacroiliac joint. A Ferguson's view is taken at 30 degrees cephalic to the pelvis and will show sacroiliitis much better than the regular AP pelvis. If further imaging is desired after normal X-rays, a CT scan is more sensitive than an MRI or bone scan. If there is some doubt regarding the diagnosis, one can repeat X-rays of the pelvis in 6 months and compare the sacroiliac joints.. Anteroposterior views with 25–30° caudal angulation of the x-ray tube, and oblique views are the most utilized in our practice, in an attempt to minimize structures overlapping, so facilitating the study interpretation.

The main limitation of the x-ray film is the low sensitivity for detecting abnormalities in the early stages of the disease. Radiographic signs in sacroiliitis appear only three to seven years after the initial symptoms onset, presenting with alterations only in the chronic phase of the disease.

The main radiographic signs are: bone erosions, joint space alterations, subchondral sclerosis and ankylosis.

CT SACROILIAC JOINT

Imaging methods like CT and MRI are extremely useful, especially in the absence of alterations, or when they are minimal on plain x-ray.

The evaluation of sacroiliitis by CT, in comparison with the conventional x-ray, has shown to be more sensitive, with a better and earlier detection of bone alterations, principally because of its capability to perform sequential slices, so avoiding structures overlapping.

The CT shows higher sensitivity for detecting minimal bone erosions and joint space narrowing, however presents the same diagnostic capacity of plain x-rays in cases of ankylosis.

The most frequent findings of sacroiliitis on CT are: joint space narrowing, subchondral sclerosis, bone erosions and ankylosis. Joint space narrowing is characterized by a thickness of less than 2.0 mm in synovial tissues. Subchondral sclerosis is found in the presence of an asymmetrical or focal area with increased density (> 5.0 mm on the iliac side, and > 3.0 mm on the sacral side). Bone erosions are small cortical defects on the synovial portion of the joint. These two latter findings can be seen in both sides of the joint, however, they are frequently seen at the iliac side because this side presents lower thickness and some cartilaginous clefts. The focal or complete fusion of the joint characterizes ankylosis observed in more advanced stages of the disease.

Alterations in the ligamentous portion are rare, when compared with the synovial portions. CT is better than MRI for detecting bone formation in the enthesis of this topography.

CT is comparable to MRI for detecting bone erosion, but is superior for evaluating bone sclerosis and ankylosis, and is indicated especially for detecting chronic alterations.

CT is a method of excellence in demonstrating bone details, besides serving as a guidance tool in percutaneous biopsies, arthrocentesis, and for intra-articular injection of steroids.

On the other hand, sacroiliac evaluations by CT presents some inconveniences like radiation exposure, and incapacity to show alterations in the acute phase, identifying especially the inflammation consequences rather than the inflammatory process activity.

SACROILIAC JOINT

The SIJ is a true diarthrodial joint that joins the sacrum to the pelvis. In this joint, hyaline cartilage on the sacral side moves against fibrocartilage on the iliac side. The joint is generally C shaped with 2 lever arms that interlock at the second sacral level. The joint contains numerous ridges and depressions, indicating its function for stability more than motion.

The sacroiliac (SI) joint has several unique anatomical features that make it one of the more challenging joints to image. The joint is difficult to profile well on radiographic views, and therefore the radiographic findings of sacroiliitis are often equivocal. Computed tomography images can usually show the findings of sacroiliitis earlier than radiographs. Magnetic resonance imaging performed with proper sequences is excellent for diagnosing even very early sacroiliitis and for following treatment response. Ankylosing spondylitis often presents with sacroiliitis, which appears as erosions, sclerosis, and joint space narrowing, eventually leading to ankylosis.

HLA B 27 TEST BY FLOWCYTOMETRY

For the flow cytometric assay, whole blood was mixed with a monoclonal anti-B27 conjugated to fluorescein-isothiocyanate (FITC) and anti-CD3 conjugated to phycoerythrin (PE). The samples were analyzed with flow cytometry by gating on CD3 positive events and anti-B27 staining intensity was evaluated as median channel fluorescence of the histogram peak. For greatest specificity, samples positive by flow cytometry should be confirmed by conventional microlymphocytotoxicity or by use of other monoclonal antibodies directed against B27.

STATISTICAL ANALYSIS

Statistical analysis was performed using the SPSS version 17.0

RESULTS

The median age at the time of the study of the 50 patients with ERA was 16 years (range 9–33 years) and the median duration of disease was 5 years (3 months–18 years). 49 patients were male and one patient was female. Median age at disease onset was 14 (8–15) years. 17(34%) of the patients were HLA B 27 positive. Three (6%) patients were in remission at the time of the study. 15 patients (30%) had joints with limitation of motion. 18 (36%) patients had decreased anterior lumbar flexion movement by modified Schober's method.

Table 1- Frequency of number of joints with limited range of motion (LOM)

Number of joints with LOM	Frequency (N = 50)	Percentage
0	35	70
1	1	2
2	6	12
3	2	4
4	2	4
5	4	8

At the time of the study, all patients were on NSAID; Indomethacin was the most commonly prescribed NSAID. 40 patients

(80%) were on it. 21 patients (42%) had received intra-articular (IA) steroid. All patients were on DMARDs at the time of the study. Sulphasalazine was the commonest DMARD used (n = 36, 64%).14 (28%) patients were on Methotrexate. Side effects of drug were seen in 7 patients. GI toxicity in 8 patients.

JADI-A

In JADI-A scoring 15 patients (30%) had damaged joints. JADI-A score varied from 1 – 6. Hip was the commonest damaged joint (n = 7; 14%), followed by knees (3, 6%), ankle (3, 6%), elbows (2, 4%). The frequency distribution of JADI-A score are shown in table 2.

Table 2 - Frequency of juvenile arthritis damage index-articular (JADI-A)-score

JADI Score	Frequency (N = 50)	Percent
0	35	70
<hr/>		
2	2	4
<hr/>		
3	4	8
<hr/>		
4	5	10
<hr/>		
5	2	4
<hr/>		
6	2	4

JADI-E

2 (4%) patients had extraarticular damage with JADI-E. None of the patients had ocular damage, severe muscular atrophy, growth failure, pubertal delay and Secondary amyloidosis.

ENTHESITIS

Ultrasound detect enthesitis in two asymptomatic individuals.

Table - 3: Active enthesitis was present in 70% of the patients.

Type of enthesitis	Frequency (N = 35)	Percentage
Achillis enthesitis	21	58.4
<hr/>		
Plantar fascitis	12	33.6
<hr/>		
Knee enthesitis	6	16.8
<hr/>		
Spine enthesitis	1	2.8
<hr/>		
Elbow enthesitis	1	2.8
<hr/>		

Polyenthesitis were present in 11 patients.

DISEASE ACTIVITY

Parent's/patient's global assessment on visual analogue scale (VAS) ranged from 0–100 mm .Median score of physician's global assessment in VAS was 30 mm (range 10–90 mm). Number of active joints varied from 1–12 (median 2.0). Duration of EMS ranged from nil to 1 hour and Median ESR was 40 (5–124) mm/hour.

DISABILITY

Mild disability in 11 (22%) patient. Median HAQ-S was 1.0 (1–3).

4 (8%) patients lost some years of education due to disease ranging from 2–10 years.

HAQ-S had correlation with limitation of spinal mobility by modified Schober's method.

HLA B27

HLA B27 was positive in 17 (34%) patients, 16 (35%) were male and 1 (2%) was female.

SACROILIAC JOINT INVOLVEMENT

18 (36%) patients had sacroiliac joint involvement in both clinical and in radiological investigations. Among these patients 12 (24%) patients were HLA B27 positive and 6 (12%) patients were HLA B27 negative.

DISCUSSION

Our study shows 70% of patients had enthesitis, compare to 60% of patients had enthesitis in Sarma.P, Misra.R, Amita Agarwal.A et al., Lucknow study⁸⁹. Presence of enthesitis had a highly significant correlation with HAQ-S in our study.

15 ERA patients had articular damage and 2 patients had extraarticular damage at a median duration of disease of 5years. Moderate limitation of movement of lumbar spine was present in 18(36%) patients. 5 (10%) patients continued to have active disease. 4(8%) patients lost some years of education due to disease ranging from 2–10 years.

More than 60% of patients lost some years of education in Lucknow study. Only 3% of patients were behind age appropriate grade in a study from Canada⁸⁹. Education level attainment of adults with JIA was similar to controls in 2 studies from UK and Finland⁸⁹.

15 patients had damaged joints in JADI-A. Hip was the commonest joint damaged in our study followed by knees, ankles and elbow. In Lucknow study hip, knees, ankle and cervical spine were more often involved. JADI-A score in our study is lower compared to the Lucknow study.⁸⁹

Sulphasalazine was the commonest DMARD used in our study, in contrast to Lucknow study in which methotrexate was the commonest DMARD.⁸⁹

The limitation of application of JADI in ERA is absence of scoring for spinal involvement. Limitation of spinal mobility had high correlation with HAQ-S. Inclusion of limitation of spinal movement in JADI may be helpful to detect early damage in ERA.

In our study 18 (36%) patients had decreased anterior lumbar flexion movement by modified Schober's method. In Lucknow study among the 49 patients, One third had limitation of lumbar spine movement by modified Schober's method.⁸⁹

HLA B27

HLA B27 was positive in 17 (34%) patients, 16 (35%) were male and 1 (2%) was female.

SACROILIAC JOINT INVOLVEMENT

18 (36%) patients had sacroiliac joint involvement in both clinical and in radiological investigations. Among these patients 12 (24%) patients were HLA B27 positive and 6 (12%) patients were HLA B27 negative.

In our study none of the patients had severe muscular atrophy, growth failure, pubertal delay, in contrast to Lucknow study in which

three patients (6.1%) had severe muscular atrophy, pubertal delay was seen in 2 (4.1%) and Secondary amyloidosis was seen in 1 (2.0%). None of the patients had ocular damage in our study similar to Lucknow study.

Our study has many limitations: numbers of patients are small, is a cross sectional study, the average disease duration is only 5 years.

CONCLUSION

- 1) Axial inflammation was common in HLA-B27 positive patients.
- 2) Functional limitations was observed in one third of the Enthesitis Related Arthritis patients.
- 3) JADI is a useful tool to measure articular and extraarticular damage in ERA.
- 4) 70% of JIA-ERA patients had enthesitis (Two third of patients had enthesitis).

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APPENDICES

*International League of Associations for Rheumatology
Classification of Juvenile Idiopathic Arthritis (JIA)*

<i>Category</i>	<i>Definition</i>	<i>Exclusions</i>
Systemic onset JIA	Arthritis in ≥ 1 joints with, or preceded by, fever of at least 2 wk duration that is documented to be daily (“quotidian”[*]) for at least 3 days and accompanied by ≥ 1 of the following:	A. Psoriasis or a history of psoriasis in the patient or a first-degree relative
	1. Evanescent (nonfixed) erythematous rash	B. Arthritis in an HLA-B27+ male beginning after the 6th birthday
	2. Generalized lymph node enlargement	C. Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis, or a history of one of these disorders in a first-degree relative
	3. Hepatomegaly or splenomegaly or both	D. Presence of IgM RF on at least 2 occasions at least 3 mo apart
	4. Serositis[†]	
Oligoarticular JIA	Arthritis affecting 1-4 joints during the first 6 mo of disease. Two subcategories are recognized:	A, B, C, D above, plus
Oligoarticular JIA	Arthritis affecting 1-4 joints during the first 6 mo of disease. Two subcategories are recognized:	A, B, C, D above, plus
	1. Persistent oligoarthritis—affecting	E. Presence of systemic JIA in the patient

<i>Category</i>	<i>Definition</i>	<i>Exclusions</i>
	≤4 joints throughout the disease course	
	2. Extended oligoarthritis—affecting >4 joints after the first 6 mo of disease	
	1. Persistent oligoarthritis—affecting ≤4 joints throughout the disease course	E. Presence of systemic JIA in the patient
	2. Extended oligoarthritis—affecting >4 joints after the first 6 mo of disease	
Polyarthritis (RF negative)	Arthritis affecting ≥5 joints during the first 6 mo of disease; a test for RF is negative	A, B, C, D, E
Polyarthritis (RF positive)	Arthritis affecting ≥5 joints during the first 6 mo of disease; ≥2 tests for RF at least 3 mo apart during the first 6 mo of disease are positive	A, B, C, E
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following:	B, C, D, E
	1. Dactylitis[‡]	
	2. Nail pitting[§] and onycholysis	
	3. Psoriasis in a first-degree relative	
Enthesitis-related arthritis	Arthritis and enthesitis,[] or arthritis or enthesitis with at least 2 of the following:	A, D, E
	1. Presence of or a history of sacroiliac joint tenderness or inflammatory lumbosacral pain or both[¶]	
	2. Presence of HLA-B27 antigen	

<i>Category</i>	<i>Definition</i>	<i>Exclusions</i>
	3. Onset of arthritis in a male >6 yr old	
	4. Acute (symptomatic) anterior uveitis	
	5. History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative	
Undifferentiated arthritis	Arthritis that fulfills criteria in no category or in ≥ 2 of the above categories	
RF, rheumatoid factor.		

* Quotidian fever is defined as a fever that rises to 39°C once a day and returns to 37°C between fever peaks.

† Serositis refers to pericarditis, pleuritis, or peritonitis, or some combination of the three.

‡ Dactylitis is swelling of ≥ 1 digits, usually in an asymmetric distribution, which extends beyond the joint margin.

§ A minimum of 2 pits on any one or more nails at any time.

|| Enthesitis is defined as tenderness at the insertion of a tendon, ligament, joint capsule, or fascia to bone.

¶ Inflammatory lumbosacral pain refers to lumbosacral pain at rest with morning stiffness that improves on movement.

MASTER CHART

<i>S.No</i>	<i>Name</i>	<i>Age/ Sex</i>	<i>Duration of Illness</i>	<i>Onset of Age</i>	<i>Peripheral Joint Involvement</i>	<i>Axial Involvement</i>	<i>Enthesitis</i>	<i>JADI -A</i>	<i>JADI -E</i>	<i>HAQ -S</i>	<i>ESR</i>	<i>CRP</i>	<i>HLA -B27</i>	<i>CT SI J</i>	<i>Developed AS</i>
1.	Murugan	15/ M	3Months	15	Yes	Yes	Yes	4	–	0.5-1.5	62	>6	+		No
2.	Sudhakar	12/ M	1 Yr	11	Yes	No	Yes	4	–	–	0	–	–	N	–
3.	Kaliyamoorthy	33/ M	18 Yr	15	Yes	Yes	No	4	2	715	30	–	+		Yes
4.	Srinivasan	16/ M	6months	15	Yes	Yes	Yes	8	–	0.5-1.5	20	–	+		Yes
5.	Balamurali	32/ M	17yrs	15yr	No	Yes	No	–	–	71.5	28	–	–		Yes
6.	Anilkumar	14/ M	24Yrs	12 yrs	Yes	No	Yes	2	–	–	5	–	–	N	–
7.	Anandh	23/ M	9 yr	4 yr	Yes		No	2	–	–	26	>6	–	N	–
8.	Lokesh	9/M	6months	9	Yes	No	Yes	6	–	–	83	60	–	N	–
9.	Dhanalakshmi	18/F	4yr	14	Yes	No	Yes	4	–	–	66	–	+	N	–

S.No	Name	Age/ Sex	Duration of Illness	Onset of Age	Peripheral Joint Involvement	Axial Involvement	Enthesitis	JADI -A	JADI -E	HAQ -S	ESR	CRP	HLA - B27	CT SI J	Developed AS
10.	Balakandan	26/ M	12 yrs	14	Yes	Yes	Yes	10	–	71.5	88	6	–		Yes
11.	Parveenkumar	24/ M	5yrs	15yrs	Yes	Yes	Yes	10	–	–	120	–	–	N	–
12.	Santhosh	16/ M	2yr	14 yrs	Yes	No	Yes	2	–	–	10	–	–	N	–
13.	Mani	13/ M	6months	14yrs				10	–	–	24	–	–	N	–
14.	Kannadasan	20/ M	6 Yrs	14yrs	Yes	Yes	Yes	10	–	0.5- 1.5	20	6	+		Yes
15.	Balaji	31/ M	23yrs	8yrs	Yes	Yes	Yes	12	–	0.5- 1.5	70	6	+		Yes
16.	Sumanth	12/ M	34yrs	9yrs	Yes	Yes	Yes	4	21	0.5- 1.5	40	–	–		Y
17.	Vasu	13/ M	5yrs	8yrs	Yes	No	Yes	4	–	–	25	–	–	–	–
18.	Velmurugan	15/ M	6months	5yr	Yes	No	Yes	10	–	–	65	–	–	–	–
19.	Saran	12/ M	3months	12	Yes	No	Yes	2	–	–	14	10	–	–	–

<i>S.No</i>	<i>Name</i>	<i>Age/ Sex</i>	<i>Duration of Illness</i>	<i>Onset of Age</i>	<i>Peripheral Joint Involvement</i>	<i>Axial Involvement</i>	<i>Enthesitis</i>	<i>JADI -A</i>	<i>JADI -E</i>	<i>HAQ -S</i>	<i>ESR</i>	<i>CRP</i>	<i>HLA - B27</i>	<i>CT SI J</i>	<i>Developed AS</i>
20.	Dakshanamoorthy	15/ M	3months	15months	Yes	No	Yes	8	-	-	25	-	-	-	-
21.	Rashak	15/ M	4months	15yrs	Yes	No	Yes	4	-	-	36	>6	+	-	-
22.	Ghouse Basha	16/ M	3yrs	13yrs	Yes	No	Yes	4	-	-	31	-	+	-	-
23.	Ramkumar	18/ M	3yrs	15yrs	Yes	Yes	Yes	2	-	-	18	29	-		
24.	Kulasekaran	14yr s	3months	14yrs	Yes	No	Yes	2	-	-	25	-	-	-	-
25.	Sekaran	19/ M	4yrs	15yrs	Yes	No	Yes	2	-	-	26	-	+		-
26.	Veeramani	19/ M	5yrs	14yrs	Yes	No	No	2	-	-	35	-	+		-
27.	Krishnamoorthy	17/ M	2yrs	15yrs	No	Yes	Yes	2	-	-	66	-	+		AS
28.	Udayakumar	22/ M	8yrs	14yrs	Yes	Yes	Yes	2	-	0.5	22	>6	-		AS
29.	Rathnakumar	19/ M	8yrs	11yrs	Yes	No	Yes	2	-	-	20	6	-	-	-

S.No	Name	Age/ Sex	Duration of Illness	Onset of Age	Peripheral Joint Involvement	Axial Involvement	Enthesitis	JADI -A	JADI -E	HAQ -S	ESR	CRP	HLA - B27	CT SI J	Developed AS
30.	Chandrasekaran	19/ M	6yrs	13yrs	Yes	No	Yes	2	–	0.5- 1.5	70	>6	+		AS
31.	Moideen	17/ M	5yrs	12yrs	Yes	No	Yes	2	–	–	30	6	–		–
32.	Elavarasan	16/ M	24yrs	14yrs	Yes	No	Yes	4	–	–	26	6	–	–	–
33.	Haribabu	23/ M	10yrs	13yrs	Yes	No	Yes	2	–	–	15	–	+		Yes
34.	Sylvester	16/ M	34yrs	13yrs	Yes	Yes	Yes	2	–	0.5- 1.5	62	–	–	–	–
35.	Shanmugam	16/ M	2months	14yrs	Yes	No	Yes	4	–	–	66	–	+		–
36.	Adaikkalam	21/ M	10yrs	11yrs	Yes	No	Yes	4	–	–	40	–	–		Yes
37.	Dineshkumar	16/ M	1yr	15yr	Yes	No	Yes	2	–	–	45	–	–		–
38.	Selvapandian	14	3month	14months	Yes	No	Yes	2	–	–	110	>6	–	–	–
39.	Gopinath	17	9yrs	8yrs	Yes	No	Yes	2	–	–	17	6	–	–	–
40.	Krishnamoorhty	17	24yrs	15yrs	Yes	Yes	Yes	4	–	–	36	6	–	–	–

<i>S.No</i>	<i>Name</i>	<i>Age/ Sex</i>	<i>Duration of Illness</i>	<i>Onset of Age</i>	<i>Peripheral Joint Involvement</i>	<i>Axial Involvement</i>	<i>Enthesitis</i>	<i>JADI -A</i>	<i>JADI -E</i>	<i>HAQ -S</i>	<i>ESR</i>	<i>CRP</i>	<i>HLA - B27</i>	<i>CT SI J</i>	<i>Developed AS</i>
41.	Vasanthakumar	17	2yrs	15yrs	Yes	Yes	Yes	6	–	–	70		–		–
42.	Selvam	18/ M	4yrs	14yrs	Yes	No	Yes	4	–	–	–	–	–	–	–
43.	Ashok	18/ M	4yrs	14yrs	Yes	Yes	Yes	4	–	–	12. 4	–	–	–	–
44.	Thangavelu	25/ M	2yr	14yr	Yes	Yes	Yes	6	–	–	16	–	–	–	–
45.	Chinappa	25/ M	10yr	15yr	Yes	Yes	Yes	2	–	–	20	–	–		–
46.	Kumaresan	13/ M	6month s	13month s	Yes	No	Yes	1	–	–	100	–	–	–	–
47.	Kunadharasan	14/ M	6month s	13 yrs	Yes	No	Yes	2	–	–	40	–	–	–	–
48.	Rasak	15/ M	4month s	4montsh	Yes	No	Yes	4	–	–	36	6	+	–	–
49.	Sarankumar	14/ M	6month s	14yrs	Yes	No	Yes	2	–	–	30	6	+	–	–
50.	Karthikeyan	13/ M	2yrs	11yrs	Yes	No	Yes	2	–	–	10	–	+		Yes



Fig -1: X-Ray Shows Normal Sacroiliac Joint



Fig-2: X-Ray Shows Bilateral Sacroilitis

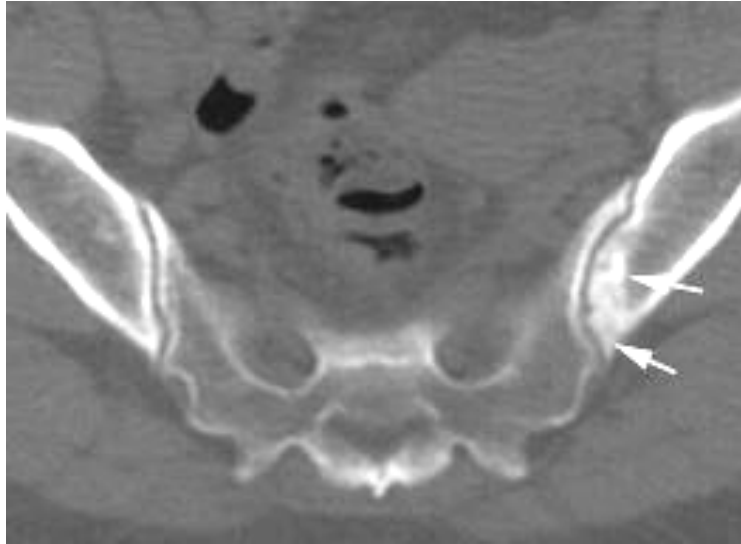


Fig-3: CT Shows Left Side Sacroilitis

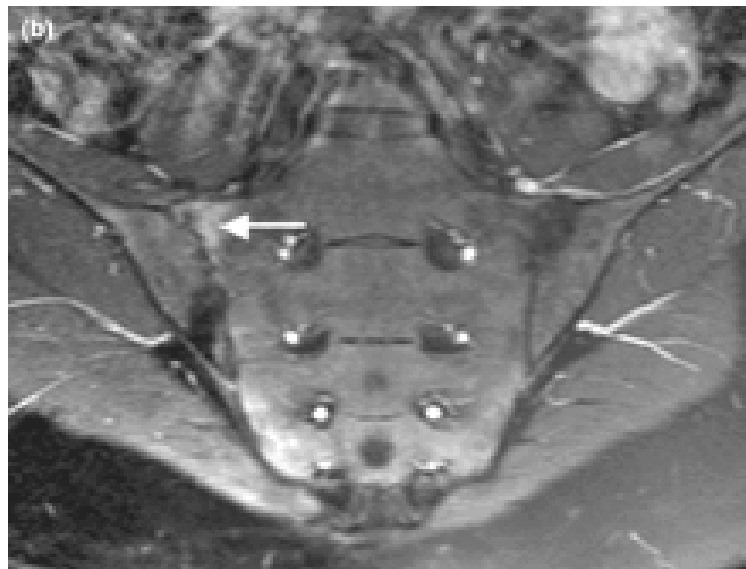


Fig-4: MRI Shows Right Side Sacroilitis



Fig-5: Ultrasound shows knee enthesitis

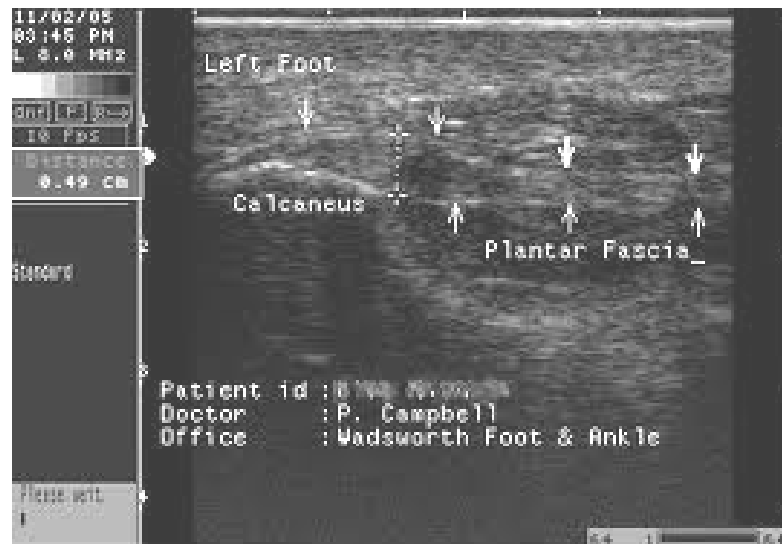


Fig- 6: Ultrasound shows plantar fasciitis



Figure - 7: Ultrasound shows achillis enthesitis

ABBREVIATION

JIA	Juvenile idiopathic arthritis
RF	Rheumatoid factor
ERA	Enthesitis related arthritis
AS	Ankylosing spondylitis
SPA	Spondyloarthropathy
HLA	Human leucocyte antigen
JADI	Juvenile articular damage index
ESR	Erythrocyte sedimentation rate
CRP	C-Reactive protein
ANA	Anti nuclear antibody
JAS	Juvenile ankylosing spondylitis
TNF	Tumor necrosis factor
NSAIDS	Nonsteroidal anti-inflammatory drugs
HAQ-S	Health assessment question-spine
DMARD	Disease modifying anti rheumatic drugs

CONSENT FORM

STUDY TITLE

A study on Outcome of Juvenile idiopathic arthritis –Enthesitis related arthritis

Study Centre : Department of Rheumatology,
Madras Medical College, Chennai – 600 003

Patient's Name :

Patient's Age :

Identification Number :

Patient may check (✓) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my complete satisfaction.

☐

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 my legal rights being affected.

☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethics committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.

☐

I agree to take part in the above study and to comply with the

☐

instructions given during the study and to faithfully co-operate with the study team, and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms.

I hereby consent to participate in this study on ‘A study on outcome of Juvenile idiopathic arthritis –Enthesitis related arthritis.

☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological and urine examination.

☐

Signature / Thumb Impression _____ Place _____
Date _____

Patient’s Name and Address: _____

Signature of the Investigator : _____ Place _____
Date _____

Study Investigator’s Name : _____

PROFORMA

STUDY ON OUTCOME OF JUVENILE IDIOPATHIC ARTHRITIS-ENTHESITIS RELATED ARTHRITIS

Name age sex

Address

Duration

Complaints

Present history

Past history

Family history

Personal history

Treatment history

General examination

Conscious febrile PR BP

Lymphadenopathy Jaundice

Eye Rash

Systemic examination

CVS RS ABD CNS

Musculoskeletal examination

Investigations

Urine routine Haemogram

CRP LFT RFT

RF ANA

HLA B-27

X-RAYS

USG

CT-SIJ

Treatment

**APPENDIX A: THE JUVENILE ARTHRITIS DAMAGE INDEX FOR ASSESSMENT OF
ARTICULAR DAMAGE (JADI-A) IN PATIENTS WITH JUVENILE IDIOPATHIC
ARTHRITIS**

THE JUVENILE ARTHRITIS DAMAGE INDEX - ARTICULAR DAMAGE						
Patient's surname:		Patient's name:				
Assessment date:		Investigator:				
<p>Definitions for scoring damage in individual joints: contractures and other joint deformities should only be scored when they are completely explained by prior damage, are not due to currently active arthritis, and are present for at least 6 months. For each joint, only the most severe lesion should be scored. Right and left temporomandibular joints, ankle and subtalar joint, and metatarsophalangeal joints of each foot are considered as a single unit. Damage is scored only if present. Damage is often irreversible and cumulative and, thus, damage scores are most frequently expected to increase or remain stable over time. However, in some cases damage scores may decline (i.e., a manifestation which was previously present which has resolved would not be scored at the time of the present assessment). In case a previous JADI evaluation is not available, information on patient's status in the preceding 6 months should be obtained from history and clinical chart.</p>						
Joint type	Definition of articular damage	Score				
Temporomandibular	Micrognathia or face asymmetry that are severe enough to cause relevant esthetic compromise and/or malalignment of the teeth arcades	1				
	Severe restriction of mouth opening (not allowing introduction of three superimposed hand fingers) with radiographic joint changes	2				
Cervical spine	Extension <50% of the normal range or cervical subluxation demonstrated radiographically	1				
	Ankylosis or history of medullary compression or surgical fusion	2				
		Right	Left			
Shoulder	External rotation <50% of the normal range and/or abduction <180° (not above the shoulder plane)	1	1			
	Ankylosis or prosthesis	2	2			
Elbow	Flexion contracture <30°	1	1			
	Flexion contracture >30°, ankylosis or prosthesis	2	2			
Wrist	Extension or flexion <50% of the normal range or subluxation or volar, ulnar or radial deviation	1	1			
	Ankylosis or prosthesis	2	2			
Metacarpophalangeal	Flexion contracture, ulnar or radial deviation = 1	I	1	2	1	2
	Subluxation, ankylosis or prosthesis = 2	II	1	2	1	2
		III	1	2	1	2
		IV	1	2	1	2
		V	1	2	1	2
Proximal interphalangeal	Flexion contracture = 1	I	1	2	1	2
	Swan neck or en boutonnière deformity or ankylosis = 2	II	1	2	1	2
		III	1	2	1	2
		IV	1	2	1	2
		V	1	2	1	2
Hip	Internal rotation <10°	1	1			
	Ankylosis or prosthesis	2	2			
Knee	Valgus deviation >15° due to arthritis or flexion contracture <25°	1	1			
	Flexion contracture >25° or prosthesis	2	2			
Ankle	Fixed valgus deformity <20°	1	1			
	Fixed valgus deformity >20°, ankylosis, arthrodesis or prosthesis	2	2			
Metatarsophalangeal	Visible deformity due to arthritis	1	1			
	Arthroplasty of the forefoot	2	2			
Total score (max 72)						

**APPENDIX B: THE JUVENILE ARTHRITIS DAMAGE INDEX FOR ASSESSMENT
OF EXTRAARTICULAR DAMAGE (JADI-E) IN PATIENTS WITH JUVENILE
IDIOPATHIC ARTHRITIS**

THE JUVENILE ARTHRITIS DAMAGE INDEX - EXTRAARTICULAR DAMAGE			
Patient's surname:		Patient's name:	
Assessment date:		Investigator:	
<p>The damage is defined as persistent changes in anatomy, physiology, pathology, or function, which may occur since the disease presentation, may result from previous disease activity or its treatment, and is present for at least 6 months. The same lesion cannot be scored twice. Damage is often irreversible and cumulative and, thus, damage scores are most frequently expected to increase or remain stable over time. However, in some cases damage scores may decline (i.e., a manifestation that was previously present which has resolved would be scored as 0 at the time of the present assessment). In case a previous JADI evaluation is not available, information on patient's status in the preceding 6 months should be obtained from history and clinical chart.</p>			
Item	Absent	Present	
OCULAR			
Cataract and/or other complications of uveitis with loss of vision (score 2 in case of ocular surgery; score 3 in case of legal blindness)	Right eye Left eye	0 0	1 2 3 1 2 3
MUSCULOSKELETAL NON-ARTICULAR			
Severe muscle atrophy	0	1	
Osteoporosis with fractures or vertebral collapse	0	1	
Avascular necrosis of bone	0	1	
Significant abnormality of the vertebral curve due to leg-length discrepancy or hip contracture	0	1	
Significant leg-length discrepancy or growth abnormality of a bone segment	0	1	
CUTANEOUS			
Striae rubrae	0	1	
Subcutaneous atrophy resulting from intraarticular corticosteroid injection	0	1	
ENDOCRINE			
Growth failure	0	1	
Pubertal delay	0	1	
Diabetes mellitus	0	1	
SECONDARY AMYLOIDOSIS	0	1	
Total score (max 17)			

சுய ஒப்புதல் படிவம்
ஆய்வு செய்யப்படும் தலைப்பு

ஜிவனைல் இடியோபதில் ஆர்த்ரைடிஸ்- என்திசைட்டிஸ் ஆர்த்ரைடிஸ்

ஆராய்ச்சி நிலையம் : மூட்டு, தசை இணைப்புத்திசு பிரிவு
இராஜீவ் காந்தி அரசு பொது மருத்துவமனை,
சென்னை மருத்துவக்கல்லூரி,
சென்னை - 3.

பங்கு பெறுபவரின் பெயர் :
பங்குபெறுபவரின் எண் :

பங்கு பெறுவர் 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 பயன்படுத்திக் கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கத்திற்கு மாறான நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன். ☐

பங்கேற்பவரின் கையொப்பம் இடம் தேதி

கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம்

ஆய்வாளரின் கையொப்பம் இடம் தேதி

INSTITUTIONAL ETHICAL COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No: 04425305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. M. Saravanan
PG in DM Rheumatology
Madras Medical College, Chennai -3

Dear Dr. M. Saravanan

The Institutional Ethical Committee of Madras Medical College reviewed and discussed your application for approval of the project / proposal / clinical trial entitled " **Outcome of Juvenile idiopathic arthritis – Enthesitis related arthritis**" No 08072010

The following members of Ethical committee were present in the meeting held on 21.07.2010 conducted at Madras Medical College,

- | | |
|---|---------------------|
| 1. Prof. S.K. Rajan, MD | -- Chairperson |
| 2. Prof. J. Mohanasundaram, MD,Ph.D,DNB
Dean, Madras Medical College, Chennai -3 | -- Deputy Chairman |
| 3. Prof. A. Sundaram, MD
Vice Principal , MMC, Chennai -3 | -- Member Secretary |
| 4. Prof. R. Sathianathan, MD
Director, Institute of Psychiatry | -- Member |
| 5. Prof R. Nandhini, MD
Director, Institute of Pharmacology, MMC, Ch-3 | -- Member |
| 6. Prof. Pregna B. Dolia , MD
Director, Institute of Biochemistry, MMC, Ch-3 | -- Member |
| 7. Prof. C. Rajendran , MD
Director, Institute of Internal Medicine, MMC, Ch-3 | -- Member |
| 8. Prof. Geetha Subramanian, MD,DM
Professor & Head , Dept. Of Cardiology | -- Member |
| 9. Prof. V. Shruti Kamal, MS
Professor of Surgery, MMC, Ch-3 | -- Member |
| 10. Prof. Md. Ali, MD, DM
Professor & Head ,Dept. of MGE, MMC, Ch-3 | -- Member |

We approve the trial 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.

