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REVIEW ARTICLE

Enthesitis-related arthritis

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Abstract Juvenile idiopathic arthritis (JIA) is the most common chronic arthritis of childhood. Currently, it is characterized by seven categories. The enthesitis-related arthritis (ERA) category usually affects boys older than 6 years and presents with lower limb asymmetrical arthritis associated with enthesitis. Later, these children can develop inflammatory lumbosacral pain (IBP). These children are at risk of developing acute anterior uveitis. A recently devised disease activity index, Juvenile Spondyloarthropathy Disease Activity Index (JSpADA), has been validated in retrospective cohorts. The corner stone of treatment is NSAIDs, local corticosteroid injections, and exercise. Methotrexate and sulfasalazine can be used for peripheral arthritis while anti-tumor necrosis factor (TNF) agents are sometimes used to treat refractory enthesitis and sacroiliitis. Almost two third of patients with ERA have persistent disease and often have impairments in their quality of life. The presence of hip or ankle arthritis and a family history of spondyloarthropathy or polyarticular joint involvement at onset are associated with poorer prognosis.

Keywords Enthesitis-related arthritis · Juvenile idiopathic arthritis · Outcomes · Pathogenesis · Prognosis · Treatment

Introduction

Juvenile idiopathic arthritis is a heterogeneous disease with seven mutually exclusive categories in the International League of Associations for Rheumatology (ILAR) classification [1]. The terminology of juvenile-onset spondyloarthropathies has evolved from the description of the syndrome of seronegative enthesopathy and arthritis in children by Rosenberg and Petty in 1982 [2], latter to the ILAR criteria which describe ERA and psoriatic arthritis as subsets, but does not mention other differentiated subsets like juvenile ankylosing spondylitis (inflammatory lumbosacral pain without other joint involvement or enthesitis), reactive arthritis, or inflammatory bowel disease-associated arthritis.

Among juvenile idiopathic arthritis (JIA), enthesitis-related arthritis (ERA) is characterized by the presence of predominantly lower limb arthritis and enthesitis in boys above the age of 6 years. In addition, these children may have inflammatory back pain and anterior uveitis [2]. Though ERA comprises only 5–10 % of JIA patients in most described cohorts [3] in India, it accounts for almost one third of children with JIA with data coming from a community-based study and hospital data [4]. A multi-ethnic cohort from Canada also suggested that ERA is the commonest category of JIA in children of Asian descent [5]. This may be due to inherent genetic differences in Asian population compared to other populations.

Pathogenesis

Similar to the other chronic arthritides of childhood, the pathogenesis of ERA is also thought to be an interplay of genetic and environmental factors. Among the genetic factors, HLA B27 has a strong association with ERA similar to other spondyloarthropathies (SpA). It is present in 65–80 % of children with ERA [3]. Besides HLA B27, an association has been found with endoplasmic reticulum aminopeptidase (ERAP-1). ERAP-1 trims the peptides for HLA class I loading in the endoplasmic reticulum after which, the HLA molecules with

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associated peptides are transported to cell surface for antigen presentation to T cell. Secondly, ERAP-1 cleaves the pro-inflammatory cytokines. The possible molecular mechanisms for the role of ERAP-1 in ERA include formation of HLA B27 homodimers due to inefficient peptide loading or presence of Cys62 in HLA B27, inappropriate antigen presentation due to improper trimming of peptides by ERAP-1 [6].

Among the environmental factors, most evidence seems to support a role for gastrointestinal microbes. Ileal biopsies and colonoscopies in patients with ERA have revealed the presence of gut inflammation. Further, almost half of the patients show enhanced lymphoproliferative response to lysates of enteric bacteria [7]. Studying the gut microbiome in patients with ERA may help in understanding the role of enteric bacteria [8].

Increased frequency of Th1 and Th17 cells with reduced number of Th2 cells in synovial fluid (SF) has been reported in ERA patients. The selective homing of Th1 cells bearing CCR5 and CXCR3 chemokine receptors could be due to high levels of interferon-inducible protein (IP-10) levels in SF of ERA patients [9].

In contrast to other forms of JIA, no autoantibodies are characteristic of ERA; thus, it seems that the innate immune system may be playing a major role. High concentrations of monocyte-derived cytokines like IL-6 and IL-1 are found in SF [10]. Monocytes from peripheral blood and SF have also been shown to express higher levels of TLR-2 and TLR-4. These cells produce more IL-6 and MMP-3 on stimulation with TLR ligands as compared to cells from healthy controls, suggesting that monocytes activated through TLRs may contribute to synovitis [11]. Recently, in spondyloarthropathy, LPS (TLR4 ligand) induced increased production of IL-23 by macrophages [12]. IL-23 drives the IL-17 production by Th17 cells. A similar mechanism may be operative in ERA. Indeed, in ERA, higher number of Th17 cells and higher levels of IL-17 are found in SF [13].

HLA B27 homodimers may be recognized by gamma delta T cells leading to IL-17 production by these innate cells. HLA B27 can interact with killer immunoglobulin-like receptor KIR3DL2 on NK and CD4 T cells [14]. Increase in KIR expression correlates with an inability of NK cells to undergo apoptosis and increased production of pro-inflammatory cytokines. Thus, the immune-pathogenesis of ERA involves a complex interaction of multiple factors and cells eventually leading to increased production of cytokines and tissue damage.

Clinical features

Enthesitis

Enthesitis is a hallmark of spondyloarthritis (SpA) with resultant pain and swelling at the entheseal sites. Positive and negative predictive values of clinical examination as compared to ultrasound as the gold standard for detecting enthesitis are 0.55 and 0.73, respectively [15]. Enthesitis may be detectable at one site during 47 % of visits and at three sites during 18 % of visits to the clinic in patients with ERA [16]. Use of pressure of 40 lb/in^2 with a dolorimeter helps standardize the pressure applied, reducing intra- and inter-observer variability. Various indices to assess enthesitis are validated for use in adult SpA; however, none of these is validated for use in children [8].

The most common sites for enthesitis in children are the patellar ligament insertion at the inferior pole of patella, the calcaneal insertions of the plantar fascia and the Achilles tendon, and the plantar fascia insertion to the metatarsal heads. Entheseal site pain and tenderness can also occur in other JIA subtypes like psoriatic arthritis and undifferentiated arthritis. In addition, tenderness or pain at or near entheseal sites can occur in children as a result of overuse or traction injuries (Osgood Schlatter syndrome, Sever's disease) and in children with fibromyalgia due to increased sensitivity to pain. Hence, not all tender points are entheseal sites. Enthesitis is a more common presenting symptom in juvenile as compared to adult SpA and has been linked with ongoing disease activity 6 months after diagnosis [8, 16]. Of note, the American College of Rheumatology (ACR) pediatric response criteria (Table 1) do not take into consideration presence or absence of enthesitis, hence limiting their use in patients with ERA [17].

Ultrasound (US) and whole-body MRI (WB MRI) are emerging as useful adjuncts to clinical examination in the diagnosis of enthesitis. As mentioned previously, US is more sensitive than clinical examination in the detection of enthesitis. US has the advantage of being noninvasive and easily accessible in the clinic; however, it is highly operator-dependent and needs specialized training, and costs and time constraints preclude its routine use in day-to-day practice. US features of enthesitis include thickening, calcification, bony erosions, and tendon hypoechogenicity; in addition, it can also demonstrate synovitis and tendinitis (Fig. 1).

Table 1 ACR pediatric response criteria

Six defined core set criteria
1. Physician global assessment of disease activity
2. Parent/patient assessment of overall well-being
3. Functional ability
4. Number of joints with active arthritis
5. Number of joints with limited range of motion
6. Erythrocyte sedimentation rate

From [17]. ACR pediatric 30, 50, 70, and 90 are defined as 30, 50, 70, and 90 % improvement, respectively, in a minimum of three core set criteria with worsening of one variable by no more than 30 %

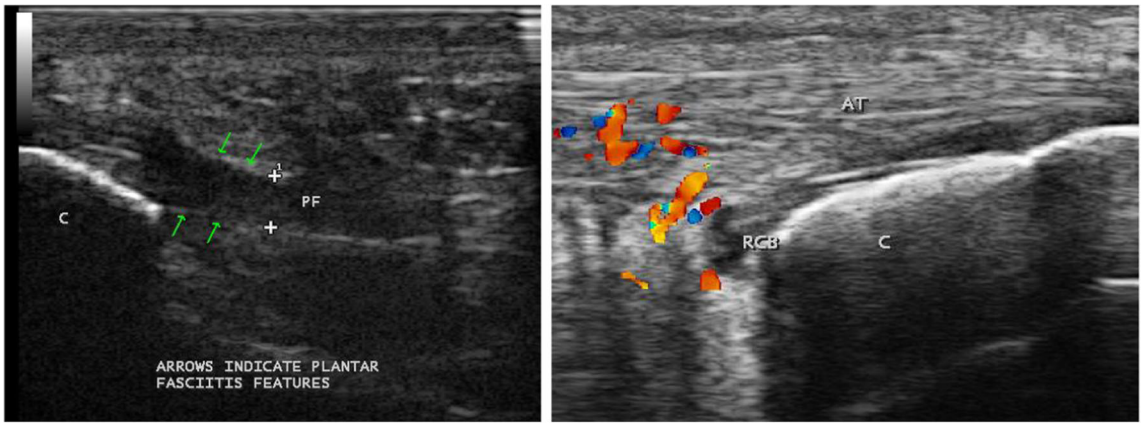

Fig. 1 US showing evidence of plantar fasciitis (PF) as increased thickness and hypo-echogenicity and the *panel* on the *right* shows vascularity in the vicinity of Achilles tendon (AT) on power Doppler (C-Calcaneum, RCB - Retrocalcaneal bursa).

Hypoechogenicity, vascularization on power Doppler, and erosions may also be documented with US in apophysitis, traction injuries, or even tender points of fibromyalgia which are differentials in the diagnosis of enthesitis in children. WB MRI using short tau inversion recovery (STIR) images has the advantage of not needing contrast administration; comparisons show that clinical examination overestimates enthesitis compared to WB MRI [8, 18].

Peripheral arthritis

Peripheral arthritis in ERA typically is asymmetric and involves large joints of lower limb. The usual joints involved are knee, hips, ankles, and tarsal joints. The joint involvement can be episodic or persistent to start with but becomes chronic over time. Tarsitis is also more common compared to other subtypes of JIA and adult SpA [8, 19]. Due to predominant involvement of lower limb, children have significant disability in getting around for school and work.

Axial arthritis

The classical feature of axial involvement is inflammatory back pain (IBP). IBP is not a common feature of ERA; although sacroiliitis may be present in 37 % of children with ERA, it can be clinically silent in 21 % [20]. Hip joint involvement is more common in ERA as compared to adult SpA and portends a poorer prognosis [21]. Hip arthritis, number of active joints, and number of entheseal sites at onset positively correlate with presence of sacroiliitis, whereas presence of dactylitis has a negative correlation with the same [20, 22].

Clinical examination (tenderness over sacroiliac joint, restricted forward flexion (Schober's test, Fig. 2), pain on flexion, abduction and external rotation—Patrick or FABER test), Gaenslen test) is less sensitive for detection of sacroiliitis in children [23]. Thus, MRI can help in early diagnosis of sacroiliitis. MRI features of active sacroiliitis are subchondral or periarticular bone marrow edema on STIR imaging or osteitis on T1 post-Gadolinium images; in the absence of bone marrow edema, the presence of enthesitis, synovitis, or capsulitis, although consistent with sacroiliitis, is not suggestive of active sacroiliitis. Preferably, a STIR image is obtained, with contrast avoided if possible in children [8, 20, 22]. Radiological sacroiliitis occurs late in patients with ERA (Fig. 3).

Extra-articular features

Acute anterior uveitis (AAU) generally presents as unilateral redness, pain, and photophobia and can be seen in 20–25 % children with ERA during follow-up. It is more common in HLA-B27-positive individuals and is the most common extra-articular feature of ERA. It is different from chronic uveitis

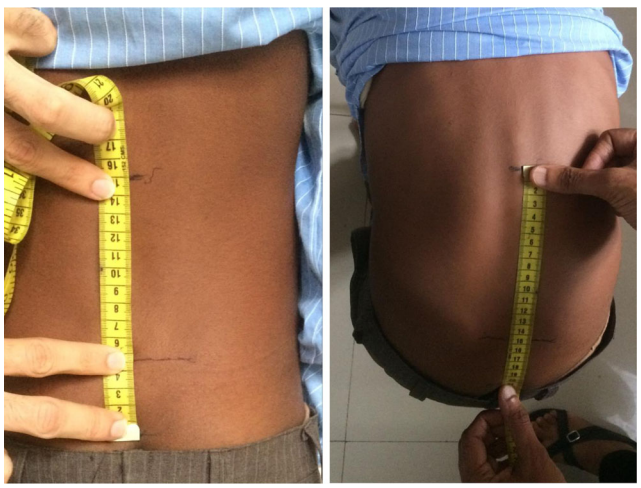

Fig. 2 Modified Schober's test: with patient standing upright, three points are marked on the back 5 cm below and 10 cm above the *horizontal line* joining the dimples of Venus. On forward flexion, keeping the knees straight, measure the skin distraction between the *top* and *bottom point*. An increase of more than 5 cm is considered normal

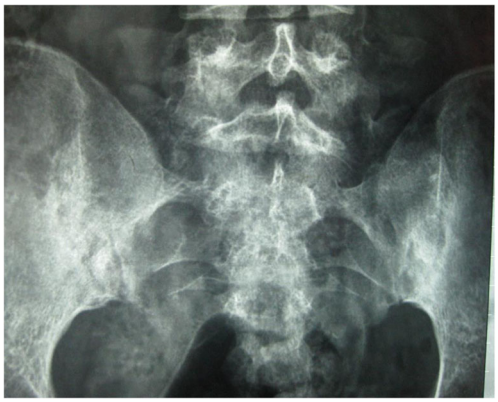

Fig. 3 Plain radiograph showing narrowing, irregularity of sacroiliac joint along with sclerosis on either side of the joint (grade III sacroiliitis)

seen in other forms of JIA which is most often asymptomatic, has higher ANA positivity, and can result in vision loss [8].

The prevalence of gut inflammation in ERA is not known. Elevated fecal calprotectin, a marker of gut inflammation, has been found in patients with ERA as compared to other JIA subtypes, healthy, or other connective tissue diseases in childhood, and such patients have been demonstrated to have a MRI evidence of gut inflammation [24].

Treatment

Patient and family education, drugs, exercise, and physical therapy form the cornerstone of management of ERA (Fig. 4) [8].

Physiotherapy and occupational therapy

Exercise and physiotherapy form the cornerstone of management of axial arthritis. After ensuring adequate pain relief using NSAIDs, patients should be instructed regarding maintenance of appropriate posture, which includes sitting up as straight as possible and keeping the spine erect while walking, lying down on a flat bed with a firm mattress, and limit use of pillow to avoid keeping the cervical spine flexed for a prolonged duration during night. In addition, avoiding frequent or prolonged bending is advisable. Patients should be advised to lie prone in the bed for at least half an hour a day. Spinal extension exercises aimed at maximizing mobility of the spine should form part of the daily routine of the patient. Home-based exercise regimens lasting 20–30 min have been proven to be effective in maintaining spinal mobility. It is best to have a physiotherapist supervise the sessions at least initially, so the patient can be taught appropriate exercises which they can then do routinely at home. Swimming is a good exercise for these patients, and the buoyancy of water has also been used in hydrotherapy and balneotherapy for patients with spondyloarthropathy. Aerobic exercise should be recommended for these patients, with a view to maintaining chest mobility as well as contributing to overall cardiovascular fitness. Patients should be advised to avoid occupations that require prolonged bending. Patients with advanced spinal mobility restriction should be careful to avoid trauma to the spine as can occur due to bumpy roads or contact sports, to minimize the risk of vertebral fractures [25, 26].

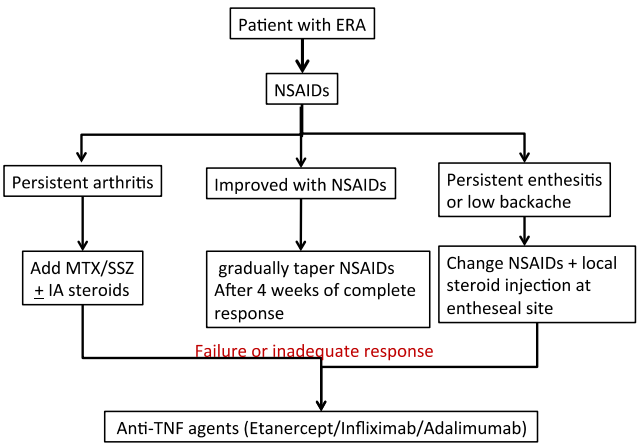

Fig. 4 Algorithm for managing a child with ERA

Anti-inflammatory drugs

NSAIDs are often used as first-line treatment for both axial and peripheral symptoms, and they reduce inflammation providing symptom relief. Usually, relief is obtained within 48 to 72 h of NSAID intake in patients with axial arthritis; however, maximal efficacy may take up to 2 weeks. Lack of efficacy at 2 weeks suggests that the NSAID is unlikely to be effective, and another NSAID should be used. There is a reasonable body of evidence to suggest that NSAIDs retard radiographic progression in adult ankylosing spondylitis (AS). It was seen that patients with AS taking continuous NSAIDs compared to on-demand NSAIDs had significantly lower radiographic progression in the spine as assessed by the modified Stoke AS Spinal Score (mSASSS). However, patients who had benefit with respect to radiographic progression were exclusively those with risk factors for spinal ankylosis, i.e., presence of spinal syndesmophytes at baseline and elevated CRP. It is unclear whether similar findings can be extrapolated to the pediatric population where radiographic changes like syndesmophytes are uncommon and axial symptoms are less common as compared to adult SpA [8, 19, 27]. However, it may be argued that if we control inflammation early, we may totally prevent radiological changes. Although the ACR guidelines for management of JIA mention NSAIDS as first-line therapy for patients with sacroiliac joint involvement or involvement of four or less joints, there is no particular preference for any particular NSAID as per recommendations. Commonly used NSAIDs are naproxen, indomethacin, and

selective COX-2 inhibitors. Naproxen has an advantage of being long acting with lesser pill burden and is used in a dose of 20–25 mg/kg/day in two divided doses. Studies in adults have consistently shown lesser cardiovascular risk with naproxen, and considering children with ERA might be on long-term NSAIDS, this merits consideration. Indomethacin is another commonly used agent, with dosing of 2.5–3 mg/kg/day in three to four divided doses. Indomethacin has the advantage of being short acting with greater potency than naproxen, tempered with the greater pill burden. Selective cyclooxygenase-2 (COX-2) inhibitors are believed to have an advantage of lesser gastrointestinal (GI) toxicity. However, it needs to be considered that children per se are at much lesser risk of GI toxicity than adults [28–30].

Corticosteroids

Systemic corticosteroids are generally not used, but local corticosteroid injections in joint or entheseal site provide excellent relief [8, 31].

Disease-modifying anti-rheumatic drugs

Methotrexate though first-line disease-modifying antirheumatic drug (DMARD) in other forms of JIA has not been tested in a randomized controlled trial in ERA. Despite the lack of evidence, ACR recommendation, which does not focus on particular subsets of JIA, but rather defines treatment algorithms based on number of joints involved and presence/absence of systemic features, suggests methotrexate use in patients with persistent arthritis. Sulfasalazine results in improvement in clinical symptoms and reduction in levels of inflammatory markers; predominant effect is on peripheral arthritis and not on axial disease or enthesitis. In children with oligoarticular or polyarticular onset of JIA, it has been shown that early treatment with sulfasalazine leads to effective long-term suppression of disease activity with better quality of life and retardation of radiologic progression. Of the 69 patients randomized to receive sulfasalazine (n=35) or placebo (n=34), 32 of the patients on sulfasalazine and 29 of those on placebo initially were followed up to 9 years. Overall, patients enrolled initially in the placebo group had longer duration of subsequent DMARD treatment with sulfasalazine or methotrexate than those initially receiving sulfasalazine. Patients initially receiving sulfasalazine had significantly better outcomes on long-term follow-up as assessed by number of active joints, patient well-being, ACR pediatric 30 response, and duration and number of episodes of complete remission off medication (CROM). At the time that this particular study was done, the classification entity of ERA was not in vogue; however, considering that patients with pauciarticular JIA have a distribution of peripheral arthritis akin to ERA, these findings are likely to be of relevance in the context of ERA.

The ACR guidelines for the management of JIA suggest use of methotrexate as first-line agent in patients with active peripheral arthritis in spite of NSAIDs and intraarticular injections. However, for patients with ERA, sulfasalazine may be preferred ahead of methotrexate [8, 28, 32, 33].

Biologic agents

Anti-tumor necrosis factor (TNF) agents infliximab [34] and etanercept [35–37] have shown improvement in arthritis and enthesitis, reduction in inflammatory markers and pain, and better physical function in open-label trials in ERA, and adalimumab has shown promising results in a double-blind , randomized placebo-controlled study in patients with juvenile-onset AS (Table 2) [38]. A recent trial in patients with ERA reported superior efficacy with etanercept in terms of reducing flare compared to placebo, in a randomized, double-blind withdrawal study design [37]. Emerging data suggests that anti-TNF agents retard radiographic progression of axial disease in AS [39]. Positive response to anti-TNF therapy is predicted in adults by short disease duration, younger age, better functional status, elevated inflammatory markers, HLA-B27 positivity, and higher spinal MRI scores [8]. It has been suggested that patients with JIA on anti-TNF therapy (etanercept) should have a complete remission on medication [40] for at least 1.5 years before considering careful tapering of the same [41]. Infliximab and etanercept use in JIA was well tolerated, and safety concerns mainly are of serious infections, including reactivation of TB and sepsis; fortunately, these are rare—one series has reported 22.8 % patients on anti-TNF agents developing infection, and only 2 out of 133 episodes of infection were severe [42, 43]. Other biologic agents such as rituximab, anakinra, abatacept, tocilizumab, secukinumab, and apremilast have not been systematically studied in patients with ERA.

Outcome

The objective assessment of disease activity in ERA remains a work in progress. Recently, the first disease activity score in juvenile spondyloarthropathy (Juvenile Spondyloarthropathy Disease Activity Score (JSpADA), including patients with ERA, juvenile psoriatic arthritis, and undifferentiated arthritis) was described and validated retrospectively in a cohort of 597 patients. It includes eight parameters (objectively scored between 0 and 1): active joint count, active enthesitis count, visual analog scale for pain, morning stiffness greater than 15 min, inflammatory markers (ESR, CRP), presence or absence of clinical sacroiliitis, uveitis (acute or chronic), and restricted lumbar spine mobility measured by modified Schober's test. This needs prospective validation across different ethnic groups [44].

Table 2 Summary of studies on anti-TNF agents in ERA

Reference no	Number of patients/ intervention	Study design	Outcome measures	Results
34	10 8 Infliximab 2 Etanercept	Retrospective review	Number of active joints Number of active entheses C-HAQ	All had remission of active joints and entheses and normalization of C-HAQ at 6 months; remission maintained till end of study period, i.e., 1 year
35	22 20 Etanercept 2 Adalimumab	Observational	ACR Pedi 30/70 CHAQ, VAS	Inactive disease in 32 % (7/22) at 3 months, 38 % (5/13) at 15 months, and 63 % (5/8) at 27 months of treatment.
36	1 Infliximab 38 Etanercept	Open label	ACR Pedi 30/50/70/90, CHAQ	Improved clinical and functional outcomes to historical placebo controls.
37	41 Etanercept	Initial open-label run-in period followed by a randomized, double-blind withdrawal design	ACR Pedi 30/50/70/90, BASDAI, BASFI, JADAS, tender entheseal sites, score for back pain.	Higher flare rate on etanercept withdrawal in responders, compared to placebo.
38	32 Adalimumab	Randomised, double-blind, placebo-controlled	ASAS20/40 ACR Pedi 30/70 BASDAI, BASFI CHAQ-DI	Superior clinical and functional outcomes compared to placebo

Early outcome analyses at 6 months showed patients with ERA to have lesser inactive disease compared to other disease subtypes [3]. More than 50 % patients of patients with ERA had no active joints at 6 months; however, only 18 % had scores of 0 for physician global assessment and 30 % for parent or patient global assessment. Three fourths of children with enthesitis at baseline continued to have enthesitis at 6 months. This represents a limitation of the existing ACR criteria for assessment of disease severity in children with ERA, as enthesitis is not included in the core set of criteria [21]. Positivity for HLA-B27 predicts the following: older age of disease onset in boys with JIA (9.3 years in HLA B27 positive versus 4.5 years in HLA B27 negative) and more active joints in the first 3 years including small joints in the lower limbs. HLA-B27 positivity predicts more IBP in first 3 years in both sexes, but increased enthesitis only in boys [45].

One of the earliest studies assessing long-term outcome (mean follow-up 11 years) in children with seronegative enthesopathy arthritis (SEA) syndrome demonstrated a variable course, with 12 out of 23 patients developing definite or possible spondyloarthropathy. Positivity for HLA-B27, presence of arthritis at presentation, and age of onset after 5 years of age were significantly associated with the development of spondyloarthropathy [40]. A 3-year study showed children with either juvenile AS or SEA (and also RF-positive polyarticular JIA) to have poorer health outcomes as compared oligoarticular JIA and RF-negative polyarticular JIA. Patients with JAS/SEA had poorest physical scores, worst parent's global assessment scores, higher pain intensity scores, and highest physician global assessment scores compared to other subtypes. Higher disability and poorer well-being within first 6 months were predictive of higher disability index at follow-up [46].

Long-term follow-up (median 15.3 years) of a cohort of 55 ERA patients from Norway showed lower levels of physical functioning, poorer physical health, and more bodily pain when compared with JIA patients with oligoarthritis or polyarthritis and healthy controls. Forty-four percent of patients with a diagnosis of ERA were in remission at the end of follow-up, with restricted lumbar flexion in 75 % and sacroiliitis in 35 %. Ankle arthritis in the first 6 months, HLA-DRB1*08 allele, and AS in a first-degree relative were predictive of failure to attain remission. Persistently high ESR and hip arthritis within the first 6 months of disease were predictive of the development of sacroiliitis. Male sex was associated with restricted anterior spinal flexion. Female sex, a family history of AS, and more joints involved in the first 6 months predicted poor physical health at 23 years. HLA-DPB1*02 allele was protective [47].

Such findings suggest a need for early aggressive treatment in patients with adverse long-term prognostic factors as family history of spondyloarthropathy, early ankle or hip

involvement, higher number of affected joints at involvement, or elevated acute phase response within first 6 months [48].

To summarize, ERA represents a significant proportion of JIA patients in the Asian population. HLA B27 is a major player in pathogenesis; innate immunity also plays a significant role. The hallmarks of disease include enthesitis, asymmetric peripheral arthritis, and inflammatory lumbosacral back pain. Exercise and NSAIDs remain the cornerstone of therapy; methotrexate and sulfasalazine are commonly used DMARDs for peripheral arthritis. Anti-TNF agents have shown promising results. A recent disease activity index (JSpADA) has been described and needs prospective validation across ethnic groups. Long-term outcomes are generally poorer than other subsets of JIA. Presence of family history of spondyloarthritis, early ankle or hip involvement, higher number of affected joints at presentation, and initial elevated acute phase response are associated with a worse prognosis.

Disclosures None.

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