Juvenile onset spondyloarthropathies: therapeutic aspects

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Juvenile onset spondyloarthropathy (SpA) is a term that refers to a group of human leucocyte antigen (HLA)-B27 associated inflammatory syndromes that affect children and adolescents under the age of 16 years and produce a continuum of clinical symptoms through adulthood. This disease group includes the seronegative enthesopathy and arthropathy (SEA) syndrome; juvenile onset anklyosing spondylitis (AS); anklylosing spondylitis; reactive arthritis (ReA); arthropathies associated with inflammatory bowel disease (IBD)—for example, Crohn's disease or ulcerative colitis; and HLA-B27-associated juvenile onset psoriatic arthritis.

The hallmarks of this disease group are enthesopathy and arthropathy (also known as tenosynovitis) affecting the peripheral joints, particularly those of the lower extremities. A significant proportion of patients will develop arthritis of the sacroiliac and spinal joints and a variety of extra-articular manifestations involving the gut, eyes, skin, and mucosa. Characteristically, IgM rheumatoid factor (IgM RF) and antinuclear antibodies (ANA) are absent in serum.

Except for some features at onset, specifically an increased prevalence of peripheral disease and the rare occurrence of axial symptoms, juvenile onset SpAs resemble adult forms of SpA in their association with HLA-B27 and bacteria, clinical expression, and radiological features. It would appear that both juvenile and adult forms of SpA share common pathogenetic mechanisms, thus providing a rationale for the same or similar therapeutic measures.

The benefits of current treatment options in juvenile onset SpA are limited to symptomatic improvement. They do not target pathogenic mechanisms and thus cannot prevent disease progression, subsequently failing to alter the long term consequences of juvenile onset SpA. However, promising outcomes of recent investigations of new immunomodulating treatments in adult forms of SpAs, particularly the anti-tumour necrosis factor α (TNFα) agents, suggest the possibility of potential new therapeutic approaches for patients with juvenile onset SpA. The inhibition of inflammatory processes by such agents in early disease may potentially prevent subsequent cartilage damage and structural changes.

Several extensive reviews of juvenile onset SpAs are available. This paper provides a brief overview of juvenile onset SpA and the treatment of the disease, with a view to potential new treatment approaches.

Epidemiology

Epidemiological data from open populations and clinical populations suggest that the prevalence, incidence, and relative frequency of juvenile onset SpA are increasing. Juvenile onset SpAs account for a significant proportion of children with juvenile arthritis. Data from paediatric rheumatology clinics in Canada, the United Kingdom, and the United States indicate that juvenile onset SpAs account for a significant proportion of children presenting with juvenile arthritis. The Canadian study estimated the annual incidence for juvenile onset SpA (excluding psoriatic arthritis) at 1.44 per 100 000 children at risk (95% confidence interval CI 1.12 to 1.87), compared with an estimated annual incidence for all forms of chronic arthritis of 4.08 (95% CI 3.62 to 4.60).

Paediatric rheumatology clinics noted an increase in the prevalence of juvenile onset SpA from 0% to 16% in the 1970s to 31% in the 1980s. This may also reflect an increase in recognition of SpA in children, distinct from other rheumatic

Abbreviations: ANA, antinuclear antibodies; AS, anklyosing spondylitis; BASDAI, Bath AS Disease Activity Index; BASFI, Bath AS Functional Index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; IL, interleukin; JCA, juvenile chronic arthritis; JRA, juvenile rheumatoid arthritis; NSAID, non-steroidal anti-inflammatory drug; ReA, reactive arthritis; RF, rheumatoid factor; SEA, seronegative enthesopathy and arthritis; SpA, spondyloarthropathy; TNFα, tumour necrosis factor α; VAS, visual analogue scale

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conditions including juvenile rheumatoid arthritis (JRA), following published descriptions in 1982 of SEA syndrome and HLA-B27 associated spondyloarthritides and enthesopathy in children. More to the less, the actual incidence of juvenile onset SpA may be higher than reported because of several undefined factors: nomenclature, criteria for diagnosis, and classification; and lack of a clear boundary between the different arthropathies of childhood. Furthermore, in the case of juvenile onset AS, in which peripheral arthritis precedes symptomatic axial arthritis by 5–10 years, the absence of apparent inflammatory or structural changes manifesting as clinical or radiographic features may lead to misdiagnosis of the disease as JRA. Thus, a large proportion of patients with juvenile onset SpA may be misdiagnosed as having JRA or juvenile chronic arthritis (JCA).

**RELATIONSHIP WITH OTHER FORMS OF JUVENILE ARTHRITIS**

Children with early onset SpA have been classified within the olioarticular/pauciarticular onset subgroups of JRA/JCA. Differential diagnosis between juvenile onset SpA and JRA/JCA includes a positive history of SpA in a first or second degree relative, high frequency of HLA-B27, male predominance (except in juvenile onset psoriatic arthritis), frequent enthesitis, peripheral arthritis asymmetrically affecting the lower extremities, and absence of ANA and IgM RF. Enthesopathy and tarsal disease in children presenting with arthritis confined to the lower extremities differentiate juvenile onset AS from JRA within one year of symptoms. Today, juvenile onset SpA is recognised as a different subset within the various forms of juvenile arthritis; recently, the term “enthesitis related arthritis” and pertinent diagnostic criteria were proposed by the International League Against Rheumatism (ILAR) Task Force Group to identify this subset of paediatric patients.

**DISEASE PROFILE**

**Pathogenesis**

The role of HLA-B27 and bacteria in disease pathogenesis appears similar to that of adult onset forms. Age related factors—for example, maturity of the immune and endocrine systems and bacterial exposure, appear to have an additional role in children. HLA-B27 and other genetic markers

Sixty to 90 per cent of patients with juvenile onset SpA have the HLA-B27 antigen. At least 20 subtypes of HLA-B27 (named consecutively from B27*01) have been identified, of which HLA-B27*05 is the subtype most commonly found in juvenile onset SpA. Non-HLA-B27 antigens may also contribute to AS in different patient populations.

HLA-B27 antigen may contribute to the pathogenesis of SpA through several proposed mechanisms: (a) presentation of bacterial antigens to CD8 lymphocytes; (b) mimicry of bacterial antigen molecules; (c) acquisition of antigenic properties after modification during bacterial infections; (d) modulation of presentation, processing, or elimination of Gram negative pathogens; and (e) interference with antigen presentation to T lymphocytes. In addition, HLA-B27 derived peptides may be presented by major histocompatibility complex class II molecules to CD4 lymphocytes. These mechanisms suggest an interaction between HLA-B27 and the T cell response, possibly triggered by a bacterial antigen, as in the case of ReA.

**Bacterial infections and arthritogenic bacteria**

In adults, enteric and non-gonococcal urogenital bacterial infections are considered important triggers in the SpAs, specifically ReA. ReA has been associated, by the detection in synovial tissues of bacteria-specific antibodies or bacterial antigens, with Salmonella, Shigella, Yersinia, and Chlamydia infections. Klebsiella has also been implicated in the aetiology of AS. These findings, together with reports of molecular mimicry between some Klebsiella, Salmonella, Yersinia, and Shigella amino acid sequences and HLA-B27, represent the primary evidence for the role of bacterial infections in the pathogenesis of SpA. In addition, increased T lymphocyte response specific for the triggering of bacterial antigens has been demonstrated in synovial fluid taken from patients with ReA. However, very few studies have examined the interaction between bacteria, HLA-B27, and other genes in children with SpA. The micro-organisms implicated more frequently in children with ReA include Salmonella spp, and Yersinia enterocolitica, but rarely Shigella flexneri, Chlamydia pneumoniae, and Chlamydia trachomatis.

**Gut**

In both children and adults, gut inflammation (in association with Crohn’s disease or ulcerative colitis) is closely linked to SpA, particularly AS and ReA. Ileocolonoscopy studies have shown that non-specific inflammatory lesions of the terminal ileum or colon mucosa occur in 75–80% of patients with JCA and are associated with a high risk of progression to AS. These findings correspond with ileocolonoscopic and clinical findings in adults with these forms of SpA. Non-specific IBD rarely causes a definitive clinical picture, but repeated histopathological and radionuclide studies of the gut may disclose acute and chronic inflammatory changes in the mucosa and submucosa of the terminal ileum and colon resembling Crohn’s disease and ulcerative colitis in more than two thirds of patients.

**Immune response**

The influence of peripheral blood and synovial fluid cells, cytokines, and cell and inflammatory mediators on the pathogenesis of SpA is the subject of continuing investigation. Cellular infiltrates in synovial tissue from peripheral and sacroiliac joints of adults with SpA show a predominance of CD4+ T lymphocytes and a significant percentage of CD14+ macrophages. TNFα, TNFβ, interferon γ, interleukin (IL)-4, IL-6, IL-12, and transforming growth factor β are also present in synovial tissue from adults and children with SpA.

In synovial tissue specimens from patients with juvenile onset SpA, expression of TNFα is prominent, consistent with high levels of TNFα mRNA seen in synovial tissues from adults with active AS. Increased production of TNFα correlates closely with increased infiltration of inflammatory cells (T cells and macrophages) into the synovia. TNFβ is also present in the synovia of patients with juvenile onset SpA, but to a smaller extent than TNFα. Increased production of these cytokines is associated with increased expression of the TNF receptor, p55, and to a smaller extent, p75. High levels of activation of CD8 cells also occur. Taken together, these findings suggest that TNF, particularly TNFα, may have a central role in mediating enhanced local inflammatory responses in juvenile onset SpA.

**CLINICAL MANIFESTATIONS**

The spectrum of disease manifestations is wide (table 1). Enthesopathy and arthropathy at peripheral sites are trademarks of juvenile onset SpA. Throughout time, the disease progresses from undifferentiated forms to differentiated SpA. Undifferentiated inflammatory conditions are characterised by peripheral enthesitis and arthritis, primarily affecting the lower limb entheses and joints, particularly the feet. This subgroup includes isolated episodes of arthritis, enthesitis, tendonitis, dactylitis, and SEA syndrome. SEA syndrome is associated with a high probability of evolution to a definite SpA, although it may also be an isolated form of juvenile onset
ability also plays a significant part in the evaluation of juvenile arthritis, by determining the functional status and monitoring radiographic changes of the feet, hips, sacroiliac joints, and spine. Functional ability may also play a significant part in the evaluation of juvenile onset SpA.**

Most patients presenting with both arthritis and enthesitis become symptomatic within the first year of diagnosis. The spine and sacroiliac joint may be affected early in the course of the disease. Arthropathy consists of tenderness, swelling, and limited joint movement, most often in the knee, mid-tarsus, and ankle, following a monoarticular or asymmetrically puciarticular pattern. Arthritis in patients with juvenile onset SpA follows a variable course, occurring as single episodes of mono- or oligoarthritis, intermittent episodes of arthritis in the joints alternating with partial or complete remission, or severe persistent disease affecting multiple joints, IBD, juvenile onset AS, or ankylosing spondarthritis. Enthesitis presents with pain and tenderness upon application of pressure, soft tissue swelling secondary to inflammation of tendon sheaths, and adjacent bursae. Enthesitis often occurs at the feet and is often severe enough to be disabling. Enthesitis follows a variable course, occurring as short term episodes of active inflammation, intermittent episodes of enthesis alternating with partial or complete remission, or severe and persistent enthesitis at multiple sites. Persistent enthesitis is associated with cortical bone erosions and joint ankylosis.

Disease activity and damage may be assessed by different methods. Joints and entheses with active inflammation as well as peripheral joint and spinal mobility are useful measures in juvenile onset SpA. Possibly, the application of a number of disease activity indices developed for adult onset populations (for example, visual analogue scale (VAS) for pain and Bath AS Disease Activity Index (BASDAI)) and for other forms of childhood arthritis (Childhood Health Assessment Questionnaire or CHAQ), may be useful. Imaging and laboratory assessment methods may include radiography, ultrasonography, and magnetic resonance, C reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Structural damage may be evaluated by determining the functional status and monitoring radiographic changes of the feet, hips, sacroiliac joints, and spine. Functional ability also plays a significant part in the evaluation of juvenile onset SpA."
or they may have recurrent episodes of enthesitis and arthritis extending to the spine and sacroiliac joints (figs 1 and 2). Others may have persistent inflammation, with severe consequences early on in the course of the disease. Changes in disease activity occur at various intervals. Chronic course is characterised by an increasing number of entheses and joints affected. The functional ability of children, adolescents, and adults with juvenile onset SpA may be severely affected by disease activity and disease damage. Patients with active disease present with diverse levels of joint-limited range of movement and interference of daily life activities. Patients with severe signs and symptoms may have significantly impaired function, which may subside during recovery.

Long term follow up of HLA-B27 children with JCA/JRA has shown that 66–75% develop sufficient clinical and radiographic signs of spondylitis and sacroiliitis to fulfil the diagnostic criteria for AS. Similarly, 70–90% of children with SEA syndrome fulfil the same criteria 5–10 years after onset. Children with Reiter's syndrome or ReA may follow a similar course, but most of them are likely to go into full remission after one episode of disease activity.

Flato et al found that disease activity for more than five years predicted disability in juvenile onset SpA. According to Minden et al, the probability of remission is only 17% after five years of disease. Nearly 60% of children with SpA have moderate to severe limitations after 10 years of disease. In comparison with adults, patients with juvenile onset AS require more hip replacements throughout the course of disease, and more patients are in functional classes III and IV. Shortly after onset, foot enthesitis and arthritis and, less commonly, ankle and knee arthritis, produce pain and severe limitations from walking or standing up. As a result, children with SpA may abandon school and stop participating in sports and social activities. Sometime later, joint stiffness, muscle atrophy, and flexure contractures contribute to functional limitations.

Structural changes of the feet and hips lead to permanent functional limitations to which spinal disease may contribute. Patients with persistent tarsitis and enthesitis develop severe structural problems, including various degrees of tarsal fusion or ankyllosing tarsitis and enthesophytosis (fig 3). Some patients develop severe problems of the spine, specifically diskitis and various deformities, which dramatically reduce their physical activity. Functional status of patients with juvenile onset SpA may reach class IV.

CURRENT TREATMENT

Treatment of juvenile onset SpA can be frustrating. Although therapeutic measures are aimed at alleviating symptoms of inflammation (that is, pain), maintaining or improving range of motion and muscle strength, preventing deformity, preserving function, and preventing or managing disease complications, short and long term results may be very unsatisfactory. Early and continuous physical and occupational therapy are critical to the patient's maintenance of independent functioning. Physical measures include resting splints for inflamed joints and orthoses to protect entheses, local application of heat or cold packs for pain relief, and exercises to improve range of motion of the spine and chest.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the initial preferred pharmacological treatment for juvenile onset SpA. Sulfasalazine may be useful in juvenile onset SpA, but differences from placebo may be only slightly significant. Short term oral corticosteroid treatment at low to moderate doses may be required to control severe episodes of arthritis; higher doses may be needed for severe enthesitis. Intrarticular corticosteroid injection (triamcinolone hexacetonide, 1 mg/kg per joint) may resolve persistent arthritis,
have a significant role in juvenile onset SpA. Recently, attention has been given to the inflammatory processes underlying rheumatic conditions as potential sites for therapeutic intervention. For SpA, high levels of the proinflammatory cytokine TNFα have been documented in synovial tissue from patients with juvenile onset SpA, and adults with active AS. TNFα is a cytokine produced mainly by monocytes and macrophages that mediates several inflammatory and immunoregulatory activities along the inflammatory cascade. Its activities include up regulation of several endothelial adhesion receptors, activation of lymphocytes and neutrophils, induction of synthesis of proinflammatory cytokines and chemokines, stimulation of other inflammatory mediators, induction of synthesis of metalloproteinases that mediate bone and cartilage destruction, and mediation of pain. In addition, TNFα has a key role in the pathogenesis of IBD, and its neutralisation by anti-TNFα has proved effective in Crohn’s disease and IBD strongly associated with AS.

Figure 3 Long term structural changes of the feet in a 20 year old patient with juvenile onset AS. (A) Dorsoplantar aspect showing metatarsophalangeal joint surface erosions and misalignment. (B) Left foot oblique view showing ankylosis of the first metatarsal and cuneal bones, metatarsophalangeal joint subluxations and enthesophytes at the margin of the 5th metatarsal-cuneal joint. (C, D) Right and left lateral views showing a spectrum of changes, including enthesophytes at the plantar fascia attachment to the calcaneus and complete fusion of the tarsal bones (ankylosing tarsitis in C and enthesophytes of the talonavicular joint in D). These previously unpublished figures are provided courtesy of Dr R Burgos-Vargas.

ANTI-TNFα THERAPY IN JUVENILE ONSET SpA

The anti-TNFα agents etanercept and infliximab have both been used in juvenile onset SpA. The effect of such agents in juvenile onset SpA can be rather striking from the clinical point of view. Using etanercept, a TNFα 75 kDa receptor IgG1 fusion protein, Reiff and Henrickson found a prolonged reduction in the number of active joints, morning stiffness, and ESR in eight patients with juvenile onset AS treated with 0.2–0.8 mg/kg subcutaneously twice weekly. The mean age of the group was 15.9 years (range 12–25), and the mean follow up of these patients was 15.4 months. All patients tolerated etanercept without side effects.

It should be noted, however, that this author (Burgos-Vargas, unpublished observations) has treated six patients with juvenile onset SpA with 5 mg/kg of infliximab (a chimeric human-murine monoclonal anti-TNFα antibody) at weeks 0, 2, 6, and then every two months for nearly a year. A remarkable reduction was found in peripheral and axial signs of disease after the first and second infusion of the drug. Improvement includes a significant decrease in the number of peripheral joints with active arthritis and tender entheses, in CRP values, in pain as evaluated by a VAS, as well as in BASDAI and BASFI scores. Interestingly, however, concurrent uveitis in one patient with juvenile onset AS seemed unresponsive to infliximab.

Although the use of anti-TNFα agents is still limited in children and adolescents with juvenile onset SpA, it seems that the effect of infliximab and etanercept in these disorders is at least as good as that seen in adult onset patients. The response appears so significant that most patients may stop NSAIDs and other drugs. Indeed, long term follow up is required to determine whether anti-TNFα agents can stop the devastating events that characterise juvenile onset SpA.

CONCLUSIONS

Juvenile onset SpA is a disorder distinct from JRA. The pathogenesis, radiological and clinical manifestations, and histopathology of the pathogenic lesions of juvenile onset SpA resemble those of the adult onset disease. Thus, treatment responses similar to those elicited in patients with adult onset SpA are expected in patients with the juvenile onset disease, and similar treatment strategies are employed in juvenile and adult onset SpA. Current treatments provide symptomatic relief but do not alter the natural course of the disease. New treatments are under investigation that target immune responses and cellular inflammatory processes which play a part in the pathogenesis of SpA. TNFα has been identified as a predominant proinflammatory cytokine in synovial tissue of patients with SpA. Clinical, histological, and immunohistochemical findings of studies of anti-TNFα antibody therapy in adult onset SpA suggest the possibility of altering the
progression of disease coincident with clinical improvement. These findings in adult onset SpA suggest that anti-TNFα therapy may confer similar benefits in juvenile onset SpA.

REFERENCES


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