A short-term follow-up of enthesitis and arthritis in the active phase of juvenile onset spondyloarthropathies

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Abstract

Objective

To describe the characteristics of enthesitis and arthritis in the active inflammatory stage of juvenile onset spondyloarthropathies (SpA) during a short-term follow-up.

Patients and methods

The study group included data of 33 patients with juvenile-onset SpA with enthesitis in ≥ 3 sites, arthritis in ≥ 4 joints, and erythrocyte sedimentation rate (ESR) of ≥ 25 mm/h despite treatment, who participated in a 26-week, double-blind, sulfasalazine versus placebo trial that showed no significant differences between groups in regard to enthesitis and arthritis.

Results

Twenty-seven boys and 6 girls (mean age: 15.3 ± 3.5 years; mean disease duration: 4.1 ± 2.7 years) with the seronegative enthesopathy and arthropathy (SEA) syndrome (n=20) or ankylosing spondylitis (AS; n=13) comprised the group. Throughout the study, the mean (± SD) number of swollen joints and tender entheses were 4.6 ± 2.5 and 8.3 ± 5.4. The entheses and joints most frequently involved were the calcaneal attachments of the plantar fascia (87.9%) and Achilles tendon (81.8%) and the ankle (87.9%) and knee (72.7%), respectively. There was pain in the cervical, thoracic, and lumbar spine in 39.4%, 69.7%, and 63.6% of patients and in the sacroiliac joints in 48.5%. Mid-foot involvement (or tarsitis) occurred in 29 patients (87.9%). Except for the feet, the simultaneous occurrence of enthesitis and arthritis in other sites was rare. Overall, there were no significant differences between SEA syndrome and AS patients.

Conclusions

Disease activity shows a significant trend for entheses and joints of the feet and a significant prevalence of axial enthesitis in juvenile onset SpA. Mid-foot involvement appears to be the most characteristic and potentially, the most severe form of disease in these patients.

Key words

Juvenile arthritis, juvenile spondyloarthropathies, juvenile ankylosing spondylitis, sea syndrome, enthesopathy, tarsitis.

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Received on July 19, 2001; accepted in revised form on April 24, 2002.

Introduction

The juvenile onset spondyloarthopathies (SpA) constitute a group of HLA-B27-associated disorders of the entheses and synovium of the joints and tendon sheaths of children and adolescents sometimes having spinal as well as sacroiliac joint disease and various extrarticular features throughout the course of the disease (1). Juvenile onset SpA includes undifferentiated and predominantly inflammatory conditions such as some isolated forms of disease and the seronegative enthesopathy and arthropathy (SEA) syndrome, as well as syndromes and diseases such as reactive arthritis (and Reiter's syndrome), psoriatic spondyloarthritis, the arthropathies of inflammatory bowel disease, and ankylosing spondylitis (AS), where definite diagnoses are made in accordance with clinical features, laboratory findings, and/or structural changes.

Enthesopathy and arthropathy of the lower extremities are the most important features of SpA (2-4). The sensitivity and specificity of enthesopathy and the involvement of the mid-foot or tarsitis allow the recognition of juvenile onset SpA and their differentiation from other forms of juvenile arthritis early on in the course of the disease (5). The distribution and course of enthesitis and arthritis in patients with juvenile onset SpA is partially known (1, 3-7). Some patients may only have a single episode of enthesitis or arthritis, but others have recurrent episodes followed by partial or complete remission or severe and persistent disease involving many entheses and joints. The long-term consequences of enthesitis include cortical bone erosions, bony proliferation, and joint ankylosis. Arthritis, on the other hand, may produce severe changes of some, but not all involved joints. In this study we have analyzed the clinical course of enthesitis and arthritis in patients with juvenile onset SpA in the active inflammatory phase of the disease over a period of six months. In particular, we evaluated the distribution and the correlation of these features with each other.

Patients and methods

Patients

The study included data from patients with juvenile onset SpA who participated in a 26-week prospective, randomized, double-blind, placebo-controlled study of sulfasalazine (SSZ) not yet published (8). In brief, such a study determined the effect of SSZ and placebo on the number of active joints as the primary variable of efficacy, and tender entheses, patient and physician assessments of efficacy and health status, severity of pain, and other parameters. Patient allocation, with no stratification according to clinical features or diagnosis, was carried out through a random-number table. Results showed improvement of most variables in both groups, but differences between them were only significant in the proportion of patients who improved according to physician and patient assessments and significant changes of concomitant therapy. Regarding peripheral enthesitis and arthritis, differences between groups were not significant.

Patients with SEA syndrome (9) and AS (10) with disease onset before the age of 16 years, age at entry < 20 years old, and active disease as defined by arthritis in ≥ 4 joints, enthesitis in ≥ 3 sites, and a erythrocyte sedimentation rate (ESR) ≥ 25 mm/h despite stable doses of non-steroidal anti-inflammatory drugs in the previous 4 weeks were included in the study.

Clinical evaluations

Peripheral and axial enthesitis and arthritis were assessed on a monthly basis for six months. These and other variables were selected by consensus by an expert committee as part of a study in progress to establish a core set of measures of disease activity in juvenile onset SpA (11). Enthesitis was defined as any grade of tenderness when pressing the tendon and ligament attachments to bone and active arthritis as any grade of soft tissue swelling and tenderness or pain when pressing or moving the joints. For the purpose of this analysis we considered three major areas of enthesitis and arthritis: 1) peripheral sites, excluding the mid foot (or tarsal area), 2) the mid-foot, and 3)

axial sites, including the spine and pelvis.

Peripheral entheses were those of the greater trochanter, patella, tibial tuberosity, calcaneal attachments of the Achilles tendon and plantar fascia, the greater tubercle of the humerus, as well as medial and lateral epicondyles. The evaluation of peripheral joints included the following: temporomandibular, shoulder, elbow, wrist, metacarpophalangeal (MCP), hip (not considering swelling), knee, ankle, metatarsophalangeal (MTP), and proximal as well as distal interphalangeal (IP) joints of the hands and feet.

Mid-foot assessment included the search for tenderness and swelling of mid-foot areas which approximately corresponded to the anatomical projection of the peroneus longus and peroneus brevis (lateral aspect), tibialis anterior and tibialis posterior (medial and dorsal aspects), extensor hallucis longus and extensor digitorum longus (dorsal aspect).

Axial entheses referred to the supraspinal ligament attachments to the spinous processes of the thoracic and lumbar spine, costosternal joints, anterosuperior and iliac crest portions of the iliac bones, and ischium. Sacroiliac joint tenderness was regarded as axial arthritis. Cervical pain and tenderness was also recorded.

Statistical analysis

In the efficacy study, data were analyzed on the basis of the intention-to-treat principle. For the analysis of baseline and final values, we used either the paired t-test or Wilcoxon's signed rank and the t-test or the Mann-Whitney test for SSZ and placebo comparisons. Significance level was fixed at $p < 0.05$. There were no significant differences between SSZ and placebo at baseline and subsequent visits in the number of active joints and tender entheses, the number of areas of foot tenderness and foot swelling, pain severity on a visual analogue scale, functional class, ESR, and anterior spinal flexion. Differences between baseline and final visit values in each of the two treatment groups were explained in part by the nature of the disease and only partially as a result of treatment. Thus, each group's enthesitis and arthritis data were pooled together in a single group data base for descriptive analysis and reported as cumulated data.

Results

The analysis included data from 33 patients (27 males and 6 females, mean ages at onset 11.7 ± 3.9 years and entry 15.9 ± 3.9 years; SEA syndrome in 20 and juvenile onset AS in 13). Mean disease duration was 4.2 ± 2.8 years. Twenty-four of 27 patients were positive for HLA-B27. None of the patients underwent intra-articular or entheseal injections of glucocorticoids or surgical procedures.

Throughout the study, active inflammation was found in a mean (± SD) of 8.3 ± 5.4 entheses and 4.6 ± 2.5 joints. In rank order, the entheses most frequently involved were those at peripheral sites, particularly the calcaneal plantar fascia and Achilles tendon attachments (Table I). In most cases peripheral enthesitis was bilateral. None of the patients had clinical signs of enthesitis in the upper extremities. There was pain in the cervical spine in 39.4% as well as tenderness at the supraspinal ligament attachments to the spinous processes of the thoracic and lumbar spine in 69.7% and 63.6% of patients. The frequency and distribution of joints with active arthritis and mid-foot areas involved are shown in Tables II and III. Ankle and MTP joint arthritis was associated with mid-foot swelling and tenderness (tarsitis) in 92% of the cases; on the other hand, 85% of the patients with tarsitis had ankle or MTP joint arthritis. In contrast to such figures, knee arthritis was associated with enthesitis around the patella or tibial tuberosity in only 5 patients; 6 other patients had enthesitis at such sites but no knee arthritis.

The comparison between patients with AS and SEA syndrome yielded no significant differences in regards to peripheral and axial signs of disease activity, including cervical pain, dorsal enthesopathy, and sacroiliac joint tenderness (Table IV).

Discussion

The periodic assessment of entheses and joints carried out in the active stage of juvenile onset SpA yields additional information on the short-term course of enthesitis and arthritis in children with SpA and highlights axial enthesitis as an important component of active disease. Although some of our data resemble previous findings (5-7), data in this study was collected according to a pre-specified format and the population studied included juvenile onset SpA patients ful-

Table I. Frequency of enthesitis throughout the study.

Entheses	n	%	Unilateral/ bilateral
Peripheral sites			
Calcaneal attachments:			
Plantar fascia	29	87.9	6/23
Achilles tendon	27	81.8	7/20
Plantar fascia, distal attachments	23	69.7	8/15
Greater trochanter	10	30.3	4/6
Patella	8	24.2	5/3
Ischium	5	15.2	2/3
Tibial tuberosity	15	45.5	7/8
Anterior iliac crest	10	30.3	2/8
Superior iliac spine	3	9.1	1/2
Axial sites			
Thoracic spine	23	69.7	NA
Lumbar spine	21	63.6	NA
Costosternal joints	13	39.4	1/12

NA: not applicable

Table II. Frequency of joints involved throughout the study.*

Site	n	%	Unilateral/ bilateral
Sacroiliac joints	16	48.5	1/15
Lower extremities			
Hip	1	3.0	0/1
Knee	24	72.7	4/20
Ankle	29	87.9	9/20
Metatarsophalangeal	21	63.6	0/21†
Proximal interphalangeal	11	33.3	10/1†
Distal interphalangeal	2	6.1	
Upper extremities			
Elbow	4	12.2	4/0
Wrist	6	18.2	5/1
Metacarpophalangeal	2	6.1	2/0
Proximal interphalangeal	2	6.1	2/0

*No patient had involvement of the temporomandibular, shoulder, or distal interphalangeal joints of the feet.
† Bilateral involvement refers to any MTP or PIP joint involved on both sides.

Table III. Frequency of mid-foot areas involved throughout the study.

Site	n	%	Unilateral/ bilateral
Tenderness			
Lateral	29	87.9	9/20
Medial	26	78.8	3/23
Dorsal	27	81.8	9/18
Swelling			
Lateral	29	87.9	5/24
Medial	28	84.8	5/24
Dorsal	20	60.6	3/17

Table IV. Frequency of axial signs of disease activity according to diagnostic categories.

	SEA syndrome (n=20)	AS (n=13)	p	OR (95% CI)
Cervical pain	6 (30.0%)	7 (53.8%)	0.17	2.7 (0.7-11.2)
Dorsal†	13 (65.0%)	10 (76.9%)	0.47	1.8 (0.4-8.0)
Lumbar†	12 (60.0%)	9 (69.2%)	0.59	1.5 (0.4-6.2)
Costosternal†	6 (30.0%)	7 (53.8%)	0.17	2.7 (0.7-11.2)
Sacroiliitis	10 (50.0%)	6 (46.1%)	0.82	0.9 (0.2-3.4)

*n (%); † Tenderness at enthesis sites.
SEA: seronegative enthesopaty; AS: ankylosing spondylitis; OR: odds ratio; CI: confidence intervals.

filling pre-specified criteria for disease activity.

Enthesopathy predominantly occurs in the lower extremities (3-7). Within one year of disease, enthesopathy is found in 83% of juvenile onset AS and 67% of undifferentiated SpA by examining non-selected patients (5-7). The calcaneal attachments of the plantar fascia and Achilles'tendon and mid-foot sites are the entheses most frequently involved. According to this study, the most important manifestations of disease activity in juvenile onset SpA occur at these entheses alongside ankle and MTP joints arthritis. Mid-foot involvement or tarsitis is particularly severe in some patients. Work in progress not published already have shown hyperintensive signals consistent with edema and inflammation in the tarsal bones, joint spaces, sheath tendons, and bursae on magnetic resonance (MR), but slight to moderate inflammation at the enthesis, tendon sheaths, or bone marrow on histology. In some patients, structural changes lead to tarsal ankylosis or ankylosing tarsitis (13).

The results of our study are relevant in regard to axial enthesitis. Regardless of diagnosis, about two-thirds of our patients had thoracic and lumbar tenderness along the supraspinous ligament attachment to the spinous process and 40% on the sacroiliac joint area. In addition, 39% had cervical pain. These findings would explain the appearance of transient complaints – axial pain, stiffness, and reduced chest expansion- in some patients (5-7, 9) and, on the other hand, indicate that in the inflammatory stage of juvenile onset SpA, enthesitis may involve both the lower extremities and axial entheses.

The possibility of biases in the combined analysis of patients who received two different treatments and patients who were classified into two diagnostic categories was considered. As mentioned before, there were no significant differences between the SSZ and placebo groups regarding peripheral and axial enthesitis and arthritis as well as the mid-foot variables despite the fact that most variables improved in the intention-to-treat analysis. As seen in adults, there was a high placebo response, which may be partially due to the natural course of the disease (14, 15).

SEA syndrome and juvenile onset AS are related forms of disease. Nearly 75% of patients with the former may evolve into AS, but regarding peripheral arthritis and enthesitis, differences between them appear minor and mostly refer to a higher prevalence of polyarthritis in patients with SEA syndrome evolving to AS (5). Because of the inclusion criteria (i.e., ≥ 4 active joints as inclusion criteria along with ≥ 3 tender entheses, and erythrocyte sedimentation rate ≥ 25 mm/h despite NSAIDS) differences between groups were less significant. At baseline, most clinical features including those involving the axial skeleton were comparable and the number of patients with AS

and SEA syndrome in the SSZ and placebo groups were balanced as well. Radiographic sacroiliitis, a feature of AS, was not included in the efficacy analysis. Interestingly, the clinical pattern and not diagnostic categories *per se* determines the response to SSZ in adult onset patients (16).

Lehtinen *et al*. (17) also analysed the data on peripheral enthesopathy recorded in patients with adult onset SpA who participated in a 26-week, double-blind, SSZ versus placebo trial. As seen in our study, there were significant improvements in most measures of disease activity, but nearly all patients had persistent enthesopathy throughout the six-month period. The calcaneal entheses – plantar fascia and Achilles tendon – were the sites most frequently involved. By ultrasonography they found 26 enthesopathic lesions showing no change, 2 new lesions, and 20 entheses that showed signs of recovery during the study. Regarding the distribution and outcome of enthesitis, our results resemble their findings to some extent.

Despite the short-term nature of this follow-up, our data may help to shed light on the clinical course of disease activity in juvenile onset SpA. The information provided could also help in the design of therapeutic trials since most therapies up to now have been centred on disease activity. Finally, it gives relevance to enthesopathy, arthropathy, and axial symptoms, the three most important features considered in current attempts to classify and diagnose this group of juvenile arthritis (18).

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