Pediatric rheumatology

Retrospective study of juvenile spondylarthropathies in Croatia over the last 11 years

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Abstract

Objectives

To determine the frequency of juvenile spondylarthropathies (JSpA) among other rheumatic diseases in a pediatric clinic population in an 11-year period in Croatia and to review their clinical, epidemiological, radiographic and laboratory features.

Methods

Of the 1264 patients with rheumatic diseases seen at a pediatric rheumatology center, 103 (8.2%) were diagnosed as having JSpA (56 boys, mean age 13.1 years, range 4.4-17.8 years), following the strict criteria of the European Spondylarthropathy Study Group. Medical history, clinical, laboratory and imaging data of the 103 patients with JSpA were analyzed.

Results

Eighty-two (79.6%) patients had undifferentiated spondylarthropathy, 6 (5.8%) patients had reactive arthritis/Reiter's disease, 6 (5.8%) had arthritis associated with inflammatory bowel disease, 5 (4.9%) had psoriatic arthritis, and only 4 (3.9%) patients had ankylosing spondylitis. The most common symptoms at the disease onset in patients with JSpA were peripheral and axial arthritis, followed by enthesitis. A significant increase in the number of patients with axial arthritis, peripheral arthritis, ocular symptoms and enthesitis was found during mean period of follow-up of 6.45 years. HLA-B27 was present in 78 (75.7%) patients.

Conclusion

In our hospital population the frequency of JSpA among other rheumatic diseases was 8.2%. The disease was equally distributed among male and female patients, with onset around the age of 13 years. Most of the patients were diagnosed with undifferentiated spondylarthropathy.

Key words

Juvenile spondylarthropathies, ankylosing spondylitis, arthritis associated with inflammatory bowel disease, psoriatic arthritis, reactive arthritis/Reiter's disease, undifferentiated spondylarthropathy, epidemiology.

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Received on January 18, 2006; accepted in revised form on February 27, 2008.

Competing interests: none declared.

Introduction

Juvenile spondylarthropathies (JSpA) comprise a group of human leukocyte antigen B27 (HLA-B27) associated rheumatic diseases with typical onset in late childhood. There are two forms of JSpA, differentiated and undifferentiated. The undifferentiated form of JSpA includes the seronegative enthesopathy and arthropathy syndrome (SEA), whereas the differentiated forms of JSpA encompass reactive arthritis/Reiter's disease, arthritis associated with inflammatory bowel disease, psoriatic arthritis and ankylosing spondylitis (1).

Although both juvenile and adult spondylarthropathies share common pathogenic mechanisms and benefit from similar therapeutic measures, JSpA presents specific features justifying a pediatric classification (2). The heterogeneity of the clinical picture in JSpA has led to several classification systems. The European Spondylarthropathy Study Group (ESSG) classification criteria are commonly used (3). Inflammatory spinal pain or asymmetrical arthritis associated with at least one additional criterion is required to satisfy the diagnosis of spondylarthropathy (3). Apart from the ESSG classification criteria for JSpA (4), the International League of Associations for Rheumatology (ILAR) proposed new diagnostic criteria. According to this classification, the JSpA are regrouped into two different categories: enthesitis-related-arthritis (ERA) and psoriatic arthritis (5). In the presence of arthritis and enthesitis, the patient will fit the ERA category. However, psoriasis and a positive family history of psoriasis will exclude the child from ERA, and some of them will be classified as psoriatic arthritis. A specific feature of the ILAR classification is the other arthritis category, where patients fitting more than one category or none are classified (6). Reactive arthritis/Reiter's disease, and arthritis associated with inflammatory bowel disease are not specifically included in the ILAR classification which is inconsistent with the traditional concept of JSpA (2).

In Croatia, there has been no hospital-based epidemiologic study of rheumatic diseases in childhood. The aim of this study was to retrospectively determine the occurrence of JSpA in pediatric rheumatology clinic population in an 11-year time-period. A further goal was to present the comprehensive review of the clinical, epidemiological, radiographic and laboratory features in this series of cases.

Patients

The study population comprised 1264 children aged 1 to 18 years, with newly diagnosed rheumatic disease during the 11-year period (January 1994 to January 2005) in the Division of Pediatric Rheumatology of the Department of Pediatrics, University Hospital Center Zagreb, Croatia. A rheumatic disease was considered a condition ordinarily cared for by a pediatric rheumatologist or a condition for which pediatric rheumatology collaboration or consultation was reasonably requested (7).

Patients with JSpA were classified according to the strict criteria of ESSG (4). They were classified into following subgroups based on published (1, 8-13) or generally accepted criteria: undifferentiated JSpA (the presence of lower axial skeleton symptoms with arthritis and/or enthesitis involving one or more sites), reactive arthritis/Reiter's disease (the presence of oligoarthritis within one month of a documented enterocolitis or urethral infection), arthritis associated with inflammatory bowel disease (arthritis, sacroiliitis, and/or enthesitis associated with Crohn's disease or ulcerative colitis confirmed by a gastroenterologist based on radiography, endoscopy, and/or histopathology), psoriatic arthritis (arthritis accompanying psoriasis, diagnosed by a dermatologist), and ankylosing spondylitis (Clinical criteria: low back pain and stiffness of at least 3 months' duration that improved by exercise and not relieved by rest, limited lumbar spinal motion in sagittal (sideways) and frontal (forward and backwards) planes, chest expansion decreased relative to normal values corrected for age and sex; Radiographic criteria: bilateral sacroiliitis grade 2 or unilateral sacroiliitis grade 3 or 4).

Medical history, clinical, and laboratory (HLA B-27, rheumatoid factor (RF) and antinuclear antibody (ANA)) data

were collected by retrospective insight into patients' medical records. Positive family history was considered when first- or second-degree relatives had diagnosis of ankylosing spondylitis, psoriasis, acute iritis, reactive arthritis, or inflammatory bowel disease. Chest expansion of less than 2.5 cm measured at the level of the fourth intercostal space has been accepted as an abnormal chest expansion (14, 15). Lumbar spinal mobility was assessed by Macrae's modification of Schober's test for which the normal values have been established for adolescent boys and girls (16, 17). Spinal mobility for children younger than 10 years of age was assessed in accordance with values adjusted for age and sex (18). Axial arthritis was defined clinically as a history of inflammatory lower back pain and/or radiographically as involvement of sacroiliac joints, spine or both (19). The determination of current or previous inflammatory back pain was based on gradual onset of symptoms persisting at least three months, improving with exercise and worsening with rest and in the morning (19). Peripheral arthritis was defined as the presence and/or history of swelling and/or restricted range of motion in at least one peripheral joint confirmed by a rheumatologist (excluding hip or shoulder) (3). Enthesitis was defined as inflammation and/or pain of peripheral entheses, such as calcaneal insertion of Achilles tendon and plantar fascia, tibial tuberositas, and costosternal junctions (20, 21). The diagnosis of sacroiliitis was established based on clinical and radiological findings. The clinical findings indicative of sacroiliitis were alternating buttock pain (22, 23). The radiographic demonstration of sacroiliitis was either unilateral or bilateral, with one or more of the following characteristics: diffuse osteoporosis of the pelvis, blurring of subchondral margins, erosions, reactive sclerosis, joint space narrowing, and fusion (14, 24). Two experienced radiologists, one of which is a specialist in musculoskeletal radiology, made the diagnosis of sacroiliitis. Ocular symptoms presented as uveitis, acute unilateral pain, photophobia, and blurring of vision. Uveitis is a general term used to define inflammation in the uveal tract, which is the middle layer of the eye (25) and it was considered to be present only if there was an ophthalmogic diagnosis of anterior uveitis. Skin changes included scaly red patches that occurred on elbows, knees and/or scalp, dactylitis, nail pitting, and psoriasis-like rash (13). Gastrointestinal symptoms were abdominal pain, diarrhea, anorexia, abdominal tenderness or palpable mass, and blood in the stools, usually accompanied by fever, weight loss, and growth retardation. Those symptoms could be initial symptoms of juvenile-onset Crohn's disease or juvenile-onset ulcerative colitis (26). Two pediatric rheumatologists interviewed and examined all subjects and assigned the diagnosis.

Patient's data from the medical records were collected and put into the relational database. While retrieving information from the medical records, which was done by the two pediatric rheumatologists, all the basic findings, such as ophthalmologist's or gastroenterologist's reports, laboratory tests, endoscopy findings, etc., were collected for every patient and the final diagnosis was revised according to the acquired data. In 7 cases the original diagnosis of JSpA was rejected in the revision process due to insufficient objective criteria found in the medical records. These patients were assigned to have other rheumatic diseases. Two cases of arthritis associated with inflammatory bowel disease were reclassified as undifferentiated spondylarthropathy due to the lack of proven Crohn's disease. Children from all over the country are referred to the Division of Pediatric Rheumatology immediately after rheumatic nature of the disease is suspected. A smaller subset of all patients (approximately 20%) with rheumatic diseases in the country is, however, treated in another hospital. Since we only had insight into the definite diagnoses of the children from the other institution, but not access to their medical records, they were not included in this study.

Descriptive statistical methods were used in data analysis and presentation. Chi-Square test was used to determine the significance of the difference between the frequencies of the groups. Fisher's exact test was used instead, whenever an expected frequency of the observation was less than 5. Alpha level less than 0.05 was considered statistically significant.

Results

Among 1264 patients with rheumatic disorders, 606 (47.9%) had juvenile idiopathic arthritis, 339 (26.8%) had collagen vascular/connective tissue rheumatic disease, 103 (8.2%) had JSpA, and 216 (17.1%) had a variety of other rheumatic diseases. Out of 103 patients with JSpA, undifferentiated spondylarthropathy was found in 82 (79.6%) patients, 6 (5.8%) patients had reactive arthritis/Reiter's disease, 6 (5.8%) had arthritis associated with inflammatory bowel disease, 5 (4.9%) had psoriatic arthritis, and only 4 (3.9%) patients had ankylosing spondylitis. No patient with JSpA was assigned a different diagnosis, nor was classified in another subgroup of JSpA during mean follow-up period of 6.45 years (range 1.8-11.5 years).

The mean patients' age at the time of diagnosis was 13.1 years (range 4.4-17.8 years). The male to female ratio was 1.2:1 (56 (54.4%) boys).

Overall, positive family history was found in 56 (54.4%) patients – in all patients with ankylosing spondylitis and psoriatic arthritis, in 53 (64.6%) patients with undifferentiated spondylarthropathy, in one of the six patients with JSpA associated with inflammatory bowel disease, and in none of the patients with reactive arthritis/Reiter's disease (Table I).

The symptoms at the disease onset and symptoms at last follow-up of each subtype of JSpA are summarized in Table II and Table III, respectively. The most common symptoms at the disease onset, as well as symptoms at last follow-up, were peripheral arthritis and axial arthritis, followed by enthesitis, found in 50 (48.5%), 39 (37.9%), and in 30 (29.1%) patients, respectively, at the disease onset, and in 77 (74.8%), 93 (90.3%), and 73 (70.9%) patients, respectively, at the end of the follow-up period. All four patients with ankylosing spondylitis had axial arthritis both at disease onset and at the last follow-up. Axial arthritis was also found

Table I. Demographic characteristics of the study group.

	Disease					
	Undifferentiated JSpA	Reiter's disease	JSpA associated with IBD	Psoriatic arthritis	Ankylosing spondylitis	Total JSpA
n (%)	82 (79.6)	6 (5.8)	6 (5.8)	5 (4.9)	4 (3.9)	103 (100)
Male:Female (%)	46:36 (56.1:43.9)	3:3 (50:50)	2:4 (33.3:66.7)	3:2 (60:40)	2:2 (50:50)	56:47 (54.4:45.6)
Mean age (years) at symptom onset ± SD (years)	13.39 ± 2.31	10.09 ± 3.53	12.73 ± 1.35	12.01 ± 3.38	15.26 ± 2.14	13.12 ± 2.36
Mean duration of follow-up (range)	8.8 (1.1-11.5)	3.8 (1.8-5.7)	7.1 (3.8-8.3)	6.5 (2.1-8.7)	4.7 (1.8-7.1)	6.45 (1.8-11.5)
Positive family history (%)	53 (64.6)	0 (0)	1 (16.7)	5 (100)	4 (100)	56 (54.4)

JSpA: juvenile spondylarthropathy; IBD: inflammatory bowel disease; SD: standard deviation.

Table II. Symptoms of 103 patients with JSpA at the disease onset.

Symptom	Disease					
	Undifferentiated JSpA (n=82)	Reiter's disease (n=6)	JSpA associated with IBD (n=6)	Psoriatic arthritis (n=5)	Ankylosing spondylitis (n=4)	Total JSpA (n=103)
Axial arthritis (%)	35 (42.7)	0 (0)	0 (0)	0 (0)	4 (100)	39 (37.9)
Peripheral arthritis (%)	41 (50)	6 (100)	2 (33.3)	1 (20)	0 (0)	50 (48.5)
Enthesitis (%)	26 (31.7)	0 (0)	1 (16.7)	0 (0)	3 (75)	30 (29.1)
Urethritis (%)	0 (0)	6 (100)	0 (0)	0 (0)	0 (0)	6 (5.8)
Gastrointestinal symptoms (%)	0 (0)	3 (50)	6 (100)	0 (0)	0 (0)	9 (8.7)
Skin changes (%)	0 (0)	0 (0)	0 (0)	5 (100)	0 (0)	5 (4.9)
Ocular symptoms (%)	2 (2.4)	6 (100)	0 (0)	0 (0)	0 (0)	8 (7.8)

JSpA: juvenile spondylarthropathy, IBD: inflammatory bowel disease.

in all 82 patients with undifferentiated JSpA at the last follow-up, while it was present in only 35 (42.7%) of these patients at the disease onset. A similar pattern was also found for enthesitis present in three (75%) and in all four patients with ankylosing spondylitis at the disease onset and at the last follow-up, respectively; while it was found in 26 (31.7%) and in 67 (81.7%) of the patients with undifferentiated JSpA at the disease onset and at the last follow-up, respectively. Peripheral arthritis was most frequent in patients with reactive arthritis/Reiter's disease at the disease onset (present in all six patients). At the last follow-up, in addition to affecting all the patients with reactive arthritis/Reiter's disease, peripheral arthritis was also found in all the patients with JSpA associated with inflammatory bowel disease and psoriatic arthritis, as well. There was significantly larger number of patients with JSpA found to have axial arthritis at the last follow-up (93 (90.3%)) than at the time of referral (39 (37.9%), $p<0.001$). The same was true for peripheral arthritis (77 (74.8%) patients at the last follow-up and 50 (48.5%) at the disease onset, $p=0.017$); enthesitis (73 (70.9%) patients at the last follow-up and 30 (29.1%) at the disease onset, $p<0.001$); and ocular symptoms (31 (30.1%) patients at the last follow-up and 8 (7.8%) at the disease onset, $p<0.001$). When the same comparison of the frequency at the disease onset and at the last follow-up was done for every subgroup of patients with JSpA, significant differences were found for axial arthritis (82 (100%) and 35 (42.7%), respectively; $p<0.001$), enthesitis (67 (81.7%) and 26 (31.7%), respectively; $p<0.001$), and ocular symptoms (24 (29.3%) and 2 (2.4%), respectively; $p<0.001$), and difference of borderline significance for peripheral arthritis (58 (70.7%) and 41 (50%), respectively; $p=0.088$) in patients with undifferentiated spondylarthropathy only. No statistically significant difference in frequency of other symptoms and signs were found in any other subgroup of JSpA ($p>0.05$).

Urethritis was found in all patients with reactive arthritis/Reiter's disease, and in no other patient in any other JSpA

Table III. Clinical characteristics of 103 patients with JSpA at last follow-up.

Symptom	Disease					
	Undifferentiated JSpA (n=82)	Reiter's disease (n=6)	JSpA associated with IBD (n=6)	Psoriatic arthritis (n=5)	Ankylosing spondylitis (n=4)	Total JSpA (n=103)
Axial arthritis	82	1	4	2	4	93
(%)	(100)	(16.7)	(66.7)	(40)	(100)	(90.3)
Peripheral arthritis	58	6	6	5	2	77
(%)	(70.7)	(100)	(100)	(100)	(50)	(74.8)
Enthesitis	67	0	2	0	4	73
(%)	(81.7)	(0)	(33.3)	(0)	(100)	(70.9)
Urethritis	0	6	0	0	0	6
(%)	(0)	(100)	(0)	(0)	(0)	(5.8)
Gastrointestinal symptoms	0	4	6	0	0	10
(%)	(0)	(75)	(100)	(0)	(0)	(9.7)
Skin changes	0	0	0	5	0	5
(%)	(0)	(0)	(0)	(100)	(0)	(4.9)
Ocular symptoms	24	6	1	0	0	31
(%)	(29.3)	(100)	(16.7)	(0)	(0)	(30.1)
Sacroiliitis	82	2	4	5	4	97
(%)	(100)	(33.3)	(66.7)	(100)	(100)	(94.2)

JSpA: juvenile spondylarthropathy, IBD: inflammatory bowel disease.

subgroup. The same was true for skin changes in patients with psoriatic arthritis. Gastrointestinal symptoms were found only in patients with JSpA associated with inflammatory bowel disease and in patients with reactive arthritis/Reiter's disease (four of the six patients in this subgroup had gastrointestinal symptoms at the last follow-up). However, gastrointestinal symptoms were found to be related to inflammatory bowel disease in former group of patients only, which was confirmed by a gastroenterologist.

Seventy-eight (75.7%) patients had HLA-B27. All patients with reactive arthritis/Reiter's disease, JSpA associated with inflammatory bowel disease, and ankylosing spondylitis, as well as 61 (74.4%) patients with undifferentiated spondylarthropathy and only one of five patients with psoriatic arthritis had positive expression of HLA-B27. ANA was found in only four (3.9%) of all patients with JSpA-two patients with reactive arthritis/Reiter's disease and two with psoriatic arthritis. RF was not found in any patient with JSpA.

Discussion

The classification of JSpA was done in accordance with the ESSG criteria, of which the major criteria are inflammatory back pain and synovitis, while enthesitis is listed as a minor one (3, 4, 27). Although, the majority of patients had axial arthritis and peripheral arthritis (90.3% and 74.8%, respectively), enthesitis was present in a great number of patients (70.9%) as well. In contrast to adults, we found enthesitis to be a common manifestation in pediatric patients (2, 28-34).

Undifferentiated forms of spondylarthropathies, identified in 79.6% of patients, were the most common among the JSpA in this study. In all these patients axial arthritis was present. All six patients with reactive arthritis/Reiter's disease had the classic triad of urethritis, arthritis, and conjunctivitis. Four of the six children with reactive arthritis/Reiter's disease had gastrointestinal symptoms prior to the onset of the classic triad, although no *Salmonella, Shigella flexneri* or *Yersinia enterocolitica* were isolated in coprocultures. *E. Coli* was, however, isolated from urine cultures in all patients. It is unclear whether this is etiologically related to the Reiter's disease, or is merely the consequence of enterocolitis or just a concomitant finding. Nevertheless, it has been reported that recurrent urinary tract infections by *E. Coli* might be triggering factor for reactive arthritis/Reiter's disease (35). However, a larger cohort of patients with reactive arthritis/Reiter's disease is warranted to investigate the possible role of *E. Coli* infection in these patients.

In this study, we found a high association of HLA-B27 expression and JSpA associated with inflammatory bowel disease with the pattern of peripheral joint involvement. This implies that genes of the HLA region have an important role in determining the clinical course of the articular disease in these patients, although not in susceptibility to inflammatory bowel disease itself (36). As in inflammatory bowel disease, the frequency of HLA-B27 in reactive arthritis/Reiter's disease in this study was also unexpectedly high. The reason for these findings could be the small number of patients with reactive arthritis/Reiter's disease and JSpA associated with inflammatory bowel disease, or the patients could have been misdiagnosed. The frequency of HLA-B27 in reactive arthritis/Reiter's disease varies from 10-83% in most adult and juvenile studies (11, 28, 36-40). The frequency of HLA-B27 in JSpA associated with inflammatory bowel disease is actually unknown, but in

adults it is reported to be 30% (41-46). Based on the finding of HLA-B27 in a great proportion of the patients in this study, it may be concluded that the expression of HLA-B27 is important in suggesting the diagnosis of JSpA, but it is not a definite diagnostic test. The frequency of HLA-B27 antigen in the present study was similar in comparison to the previously published work (60-90%) (1, 28, 47-49).

Enthesitis was a characteristic early manifestation of ankylosing spondylitis present in all four patients. All of them had axial arthritis as the initial symptom, although in the literature it is usually absent at disease onset, but becomes evident during disease course (43, 50, 51). It may be that ankylosing spondylitis was diagnosed in the late stages of the disease in these cases. The reason for the high prevalence of axial arthritis in undifferentiated JSpA group of patients could be the wrong labelling of patients with ankylosing spondylitis. This is, however, unlikely, since the diagnosis was made by consensus of two pediatric rheumatologists. Another explanation could be the evolution of the undifferentiated JSpA to ankylosing spondylitis in a fraction of patients in the later stages of the disease.

In previous studies, it has been noted that most patients with JSpA start with peripheral arthritis and only few with axial symptoms (39, 50, 51). The same was true in our study in which more patients with peripheral arthritis than axial arthritis was found on the first referral, thus accentuating the finding of peripheral joints involvement as early indicator of JSpA.

Sacroiliitis was diagnosed based on clinical (alternating buttock pain) and radiological findings. Radiological sacroiliitis of at least grade 2 bilaterally is an obligatory criterion for definite ankylosing spondylitis (10). Therefore, all those patients who had sacroiliac joint pain and radiographic sacroiliitis below the cut off level for ankylosing spondylitis (grade less than 2 bilateral or grade less than 3 unilateral) could not be categorized as having ankylosing spondylitis, but still we considered them as having sacroiliitis. Our study showed that sacroiliitis was present in 94.2% of patients. It was diagnosed using conventional radiography in all cases. Since the final diagnosis of ankylosing spondylitis requires the demonstration of radiological sacroiliitis which becomes manifest 5-10 years after the onset of the disease (33, 52-55), patients should be followed for that period of time before the final diagnosis was made, and in our study the mean time of follow up was 6.45 years. Undifferentiated spondylarthropathy constitute a subgroup of JSpA in which patients fulfill the ESSG classification criteria (3), but not specific criteria for ankylosing spondylitis, reactive arthritis, psoriatic arthritis, or JSpA associated with inflammatory bowel disease. Later in the course of disease, a clearer clinical picture of JSpA might develop. In the study of patients with possible early ankylosing spondylitis, Mau *et al* (52) showed that ankylosing spondylitis developed in 70% and undifferentiated spondylarthropathy in another 20% of 41 HLA-B27 positive patients available for follow-up after 10 years. Magnetic resonance imaging (MRI) would definitely improve the faster diagnosis, since pathologic changes in the sacroiliac joints can be demonstrated earlier with MRI than with conventional radiographs (56). The value of an early diagnosis is the chance of early classification into the JSpA subgroup with the possible impact on therapy, because early treatment is likely to improve immunologically mediated diseases in which self-perpetuation of inflammation is an important pathophysiologic mechanism (23).

The limitation of our study was the fact that all the patients with JSpA in the country were not treated in our institution; nevertheless a significantly smaller number of patients are referred in another hospital and the frequency of certain rheumatic diseases in that population of children was similar to our study group.

Based on the data from the registers of pediatric rheumatology clinics in Canada, UK and USA, it was reported that approximately 7.9-9.8% of all children referred to the clinics have spondylarthropathy (57-59). Our study showed similar prevalence (8.2%) of JSpA among other rheumatic diseases of childhood and adolescence. A multidisciplinary team in a pediatric environment should be responsible for the management of children with JSpA to ensure the best care for these children with their chronic disease and risk of long-term disability (2).

Conclusions

This hospital-based study found the frequency of JSpA among other rheumatic diseases to be 8.2%. Both sexes were equally affected, with the mean age of disease onset of 13.1 years. The most common form of the disease in this study was undifferentiated JSpA. The most frequent symptoms found both at disease onset and after mean time of follow-up of 6.45 years were peripheral arthritis, axial arthritis, and enthesitis. Expression of HLA-B27 was found in 75.5% of the patients.

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