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Clinical Characteristics of Patients with Spondyloarthritides and HLA-B27 Positive Antigen

Marija Glasnović[1], Ivica Bošnjak[1], Miroslav Šram[1], Željko Vranješ[2], Aleksandar Včev[1], Blaženka Dobrošević[3], Jasminka Sinčić Petričević[1], Elizabeta Horvatić[4], Želimir Orkić[5], Refmir Tadžić[6], Anamarija Soldo[7], Dina Šišljagić[7] and Kristijan Dinjar[8]

[1] »J. J. Strossmayer« University, Osijek University Hospital Center, Clinic for Internal Medicine, Osijek, Croatia
[2] »J. J. Strossmayer« University, Osijek University Hospital Center, Department of Othorynolaringology and Neck Surgery, Osijek, Croatia
[3] »J. J. Strossmayer« University, Osijek University Hospital Center, Department for Medical Biochemistry, Osijek, Croatia
[4] »Tomislav Bardek« General Hospital, Department of Pathology and Cytology, Koprivnica, Croatia
[5] »J. J. Strossmayer« University, Osijek University Hospital Center, Department of Plastic Surgery, Osijek, Croatia
[6] Health Center, Hamburg, Germany
[7] »J. J. Strossmayer« University, Osijek University Hospital Center, General Practice Health Center, Osijek, Croatia
[8] »J. J. Strossmayer« University, Osijek University Hospital Center, Department of Oral and Maxillofacial surgery, Osijek, Croatia

A B S T R A C T

The aim of this study was to present our experiences in diagnosing spondyloarthritides (SpA), and to list the most common clinical features of HLA-B 27 positive patients.The study included 65 HLA-B 27 positive patients with confirmed diagnosis of ankylosing spondylitis(AS) and psoriatic arthritis (PsA) who were analyzed between 2009 and 2010 in Clinic of Internal Medicine in Osijek. The diagnosis of seronegative spondyloarthritides was based on the ASAS (Assessment in AS Working Group) classification criteria for axial and then supplemented with ASAS criteria for peripheral SpA and was confirmed by radiological techniques. For diagnosing the ankylosing spondylitis (AS), there have been applied the modified New York criteria. Radiological criteria for definite sacroiliitis according to the modified New York criteria is bilateral sacroiliitis, grade 2–4 (≥2) or unilateral sacroiliitis, grade 3–4. For diagnosing the psoriatic arthritis (PsA), there were used CASPAR diagnostic criteria. Other features of SpA are defined within the existing classification criteria. HLA-B27 antigen was determined by direct immune-fluorescence technique using flow cytometer. The average age of patients was 50.34 years, of whom 27 female (41.53%), 38 male (58.46%). Duration of illness was 15.79 years on average. With 75.38% of patients, there had been determined the diagnosis of AS; 24.62% of patients had the diagnosis of PsA. The most common clinical characteristics that patients had were: inflammatory back pain (pain Inflammation along the lumbosacral spine), peripheral arthritis, intermittent pain in the gluteus, sacroiliitis, enthesitis, uveitis, dactilitis.

Key words: *Spondyloarthtritides, HLA-B27,antigen, ASAS classification criteria*

Introduction

Spondyloarthritides (SpA) are a group of inflammatory rheumatic diseases with several common clinical, radiological immonogentic characteristics. To this group of diseases, there might be included: ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA) including Reiter's syndrome too, enteropathic spondyloarthritis (spondyloarthritis associated with inflammatory bowel disease, usually with Crohn disease and ulcerative arthritis) and undifferentiated spondyloarthropathies (with SpA), since with some patients there might not be established precise diagnosis because of mutually overlapping symptoms and signs of several SpA. This is the family of different sorts of arthritis having common clinical features (inflammatory process in the axial skeleton and/or peripheral arthritis) and radiological features (sacroiliitis and/or enthesopathia), associated with the

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HLA-B27 gentic predisposition factor. Presence of HLA--B27 gen can be used as one of the markers for this group of diseases.Common feature of all diseases with this group is a negative finding of RF in the blood, and rather often occurrence of disease among close relatives. Clinical SpA features that help in the diagnosing of specific SpA are: inflammatory back pain (IBP), peripheral arthritis (usually asymmetrical), enthesitis (as most frequent clinical features of SpA), sacroiliitis, dactilitis (less often than enthesitis and more frequent in ReA and PsA). Extra-articular manifestations are: uveitis (usually acute, anterior, unilateral and recurrent), inflammatory bowel disease (IBD) and psoriasis. Dactilitis or IBD present recognizable domain of SpA The aim of our study was to evaluate the clinical features of patients with SpA having positive HLA-B27 antigen.

Subjects and Methods

The study included 65 patients with established diagnosis of seronegative spondyloarthritides (SpA) and with ankylosing spondylitis (AS) and psoriatic arthritis (PsA) who were analyzed between 2009 and 2010 in Clinic of Internal Medicine in Osijek. The SpA diagnosis was based on ASAS (Assessment in AS Working Group) classification criteria for axial and peripheral SpA[1] – Figure 1 and 2, and was confirmed by radiological techniques. For diagnosing of ankylosing spondylitis (AS), there were applied the modified New York criteria[2], while for diagnosing PsA, there were used CASPAR diagnostic criteria[3]. Other features of SpA are defined within the existing classification criteria.

HLA-B27 antigen was determined by direct immunofluorescence technique using FACSCalibur flow cytometer (BD). The data were analyzed with HLA_B27 software (BD Biosciences).

The data were analyzed with Microsoft Excel program.

Results

The study included 49 patients with confirmed diagnosis of ankylosing spondylitis (AS) of which 17 female (34.69%) and 32 male (65.31%). The average age was 49.86 years. Duration of illness was 13.65 years at average. The study also included 16 patients totally, all having psoriatic arthritis (PsA), i.e. 10 female (62.50%) and 6 male (37.50%) Average age of these patients was 50.82 years. Duration of disease was 17.94 years at average. All patients with PsA had an existing psoriasis (100%) (Table 1). As the most common clinical feature of patients with ankylosing spondylitis (AS)-inflammatory back pain (inflammatory back pain (IBP) was present with 46 patients (93.87%). Elevated ESR/CRP were determined with 25 patients (51.02%). Sacroiliitis had 45 patients (91.83%), of which bilateral 75.50%, 24.50% unilateral. Alternating gluteal pain had 35 patients (71.42%). Enthesitis had 17 patients (34.69%); most frequently in heels (58.82%). Uveitis had 12 patients (24.48%). Two patients had Crohn's disease/IBD (4.08%), while a positive family anamnesis appeared with 29 patients (59.18%). A good response to the application of nonsteroidal anti-inflammatory drugs (NSAIDs) had 40 patients (81.63%) (Table 2). Peripheral arthritis occurred with 11 patients (22.44%) of which most frequently there were affected knee joints (54.50%), hips (18.18%), fists (18.18%) and shoulders (9.09%). Involvement of the axial skeleton as »bamboo spine« was present with 9 patients (18.36%) (Table 3). Inflammatory low back pain as most common clinical feature with patients having psoriatic arthritis (PsA) had 10 patients (62.50%). Sacroiliitis had 6 patients (37.60%) of which bilateral (33.40%), unilateral (66.60%). Alternating pain in gluteus had 7 patients (43.75%). Enthesitis had 5 patients (31.25%), mostly in heels (60%), dactilitis had 6 patients (37.50%). Elevated ESR/CRP had 5 patients (31.25%). A positive family anamnesis happened with 6 patients (37.50%). Good response to

Arthritis or enthesitis or dactilitis plus	
≥1 SpA feature	≥2 other spa features
• Uveitis	• Arthritis
• Psoriasis	• Enthesitis
• Crohn / colitis	• Dactilitis
• Previous infection	• Inflammatory low back pain
• HLA-B27 +	• Family history for spa
• Sacroiliitis	

Fig. 2. ASAS classification criteria for peripheral SpA. According to Rudwaleit M et al.[18] Ann Rheum Dis 70 (2011) 25

Sacroiliitis plus ≥1 SpA features:	or:	HLA-B 27 plus ≥2 other SpA features
IBP (Inflammatory back pain)		Sacroiliitis on imaging diagnostic methods
** ES (Peripheral arthritis, Enthesitis (heel)		
Acute anterior uveitis, Dactilitis, Psoriasis, Chron / UC)		Active (acute) inflammation on MR-
Good response to NSAIDs		Sacroiliitis
Family history for SpA		or
HLA -B27 pos		Definite radiographic sacroiliitis according to the New York criteria
Elevated ESR or CRP		
(** Extra-spinal disease)		

Fig. 1. ASAS classification criteria for axial SpA. According to Rudwaleit M et al.[1] Ann Rheum Dis. 68(6) (2009) 777.

TABLE 1
DEMOGRAPHIC DATA OF PATIENTS WITH MOST COMMON SPA

Diagnosis	Gender		Average age	Disease duration
	M	F		
AS 49 (75.38%)	32 (65.31%)	17 (34.69%)	49.86 years	13.65 years
PsA 16 (24.62%)	6 (37.50%)	10 (62.50%)	50.82 years	17.94 years

TABLE 2
COMMON CLINICAL CHARACTERISTICS OF PATIENTS WITH AS

General characteristics of patients	Number of patients 49	%
Inflammatory low back pain (IBP)	46	93.87
Sacroiliitis	45	91.83
Sacroiliitis unilateral	11	24.50
Sacroiliitis bilateral	34	75.50
Bamboo spine	9	18.36
Peripheral arthritis	11	22.44
Alternating pain in the gluteal	35	71.42
Uveitis	12	24.48
Enthesitis	17	34.69
Dactilitis	0	0.00
Crohn's disease / IBD	2	4.08
Good response to NSAIDs	40	81.63
Elevated ESR / CRP	25	51.02
Positive family history for SpA	29	59.18

TABLE 3
PERIPHERAL ARTHRITIS AND CHANGES IN THE AXIAL SKELETON IN AS

The area of involvement of peripheral arthritis	Number of patients 11	% 22.44
Hips	2	18.18
Knees	6	54.50
Fists	2	18.18
Shoulders	1	9.09
Axial skeleton	9	18.36
Bamboo spine		

NSAIDs had 10 patients (62.50%) (Table 4). All patients with PsA had peripheral arthritis, i.e. in their fists (62.50%) and knees (37.50%) (Table 5).

Discussion

Ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are the most important representatives of the SpA entity group. With the population, frequency of disease is positively correlated with frequency of HLA-B27 antigen. Inflammatory low back pain is the leading symptom of axial SpA and AS, and in order to determine the diagnosis of inflammatory back pain, it is necessary to meet the standard criteria. Proof of radiological sacroiliitis is the key for diagnosis to New York criteria in AS. Important, early symptoms of axial SpA are development of chronic back pain and morning stiffness, usually in early adulthood. The pain is dull and localized deeply in the gluteal region, and in later phase, in the lower part of the LS spine. Diagnosis of inflammatory back pain (IBP) was reestablished with people younger than 45 years of age, accompanied by insidious onset of symptoms lasting > 3 months, morning stiffness lasting > 30 minutes, having favorable effect of exercises upon standstill phase[4].

TABLE 4
COMMON CLINICAL CHARACTERISTICS OF PATIENTS WITH PSA

General characteristics of patients	Number of patients 16	%
Inflammatory low back pain (IBP)	10	62.50
Sacroilitis	6	37.60
Bilateral sacroiliitis	2	33.40
Unilateral sacroiliitis	4	66.60
Peripheral arthritis	16	100.00
Alternating pain in the gluteal	7	43.75
Enthesitis	5	31.25
Dactilitis	6	37.50
Psoriasis	16	100.00
Good response to NSAIDs	10	62.50
Elevated ESR / CRP	5	31.25
Positive family anamnesis to SpA	6	37.50

TABLE 5
PERIPHERAL ARTHRITIS WITH PSA

Affected area	Number of patients 16	% 100
Fists	10	62.50
Knees	6	37.50

According to criteria of the European Study Group of spondyloarthropathies (ESSG) from the year 1995, diagnosis of AS with a sensitivity of > 90 %, was possible to be set based on inflammatory pain in the lumbosacral area or along the spine and bilateral radiological sacroiliitis[5]. However, the presence of inflammatory pain itself, presents insufficient findings for early diagnosis of

AS. Typical inflammatory pain in the lumbosacral spine in the early AS, is present with approximately 70–80% patients, and might be found with 20–25% of patients having mechanical pain in their backs. Therefore, in the algorithm for establishing an early and reliable diagnosis of AS, there had been proposed combination of significant clinical, laboratory investigations, with a probability degree of 80% to 90%[6,7]. In the definition of axial SpA, especially with younger patients having inflammatory low back pain (LBP), while it is difficult to establish AS diagnosis by a radiological procedure, new guidelines are of importance, which, back in 2009 were brought by the International Working Group of eminent rheumatologists, so called ASAS classification criteria for axial SpA[1]. New ASAS classification criteria for peripheral SpA, are also applicable to SpA patients having peripheral arthritis, enthesitis and/or dactilitis[1].

The most frequent spondyloarthritides (SpA) is ankylosing spondylitis (AS). The prevalence of disease amounts 0.2–1.4%, and is more common with male patients. Frequency of disease is positively correlated with the HLA-B27 positive antigen (90–95%). Disease starts with 15 to 40 years of age. In our study, inflammatory low back pain (IBP) with patients having AS, had 46 (93.97%) of them. Of total number of 49 patients with confirmed AS diagnosis, according to the ASAS criteria, 17 were women (34.69%) and 32 men (65.31%). The average age was 49.86 years. All patients had positive HLA-B27 antigen. In 75% cases of HLA-B27 positive patients, AS started in the sacroiliac joint or SI joint and then spread to other structures of the spine, annexation, ligaments. Radiology criteria for definite sacroilitiis, which brings erosion and sclerosis according to the modified New York criteria, is bilateral sacroiliitis grade 2–4 (≥ 2), or unilateral sacroiliitis grade 3–4[8]. Sacroiliitis in AS is more frequently symmetrical. Radiological absence of arthritis in an early stage of the disease when there are no subjective symptoms is the reason of overdue establishment of diagnosis, and this delay amounts 8–10 years at average. Patients with early AS, per the level of disease activity, quality of life and response to treatment did not differ from patients having radiological sacroiliitis. By latter-day methods of CT and MRI there might be detected changes in SI joints, even before detection of the radiological changes. MRI is a reliable method for diagnosing, in pre-radiological stage, the sacroiliatic arthritis and might be used to monitor the achieved effect of treatment by biological therapy[9]. With our patients having AS, there had been found sacroiliitis with 45 patients (91.83%), of which 34 patients (75.50%) had bilateral sacroiliitis, while unilateral sacroiliitis had 11 patients (24.50%). Pursuant to MRI, with 4 (8.16%) patients having AS, we found sacroiliitis in pre-radiological phase of disease. The course of AS is highly variable and characterized by spontaneous remissions and exacerbations. In its natural course, the disease affects all three segments of the spine and ends with ossification of tendon and ligament insertions, leading to ankylosis of joints and by-pass of whorls with radiological images – »bamboo spine«[10]. In our study, involvement of the axial skeleton as »bamboo spine« appeared with 9 patients, i.e. 18.36%. Pathological changes (inflammation) at vertex the tendon, fascia, ligament to bone (enthesitis), is the epicenter of initial pathohistological changes and the primary lesion in SpA. Peripheral enthesitis may be observed in all forms of SpA, including the undifferentiated forms, and might, for a longer period of time, be the only manifestation of HLA-B27 positive patients with SpA. The most common symptoms are pain in the heel, swelling within the mid part of foot and pain around knee. Chronic inflammation of enthesis might lead to formation of bone spikes (excessive bone growth) that causes heel pain[11]. Ultrasound (US) imaging and magnetic resonance imaging (MRI), confirm that enthesitis is the primary lesion of SpA. Damage intensity and therapeutic response can be monitored by the use of MRI. In our study, with patients having established diagnosis of AS, there were 17 patients with enthesitis (34.69%) and usually epicenter was in heel (58.82%). Uveitis in 19–88% correlated with the HLA-B27 phenotype. Uvea feeds the eye through blood vessels and, therefore, the eye illness brings in question the diet of the eye in whole. Acute anterior uveitis might occur as a distinct clinical entity or in conjunction with SpA. Characteristics of anterior uveitis in SpA are: acute onset, it is unilateral, recurrent, associated with HLA-B27 Ag (19–88%), has spontaneous remissions[12]. In our study, 12 patients (24.48%) with AS had recurrent uveitis, which coincides with the findings of the study. In AS, there had been found inflammatory arthritis, asymmetric, predominantly with lower limbs. Peripheral arthritis occurred with 11 patients (22.44%) of which mostly affected were knee joints 54.50%, hip joints 18.18%, fists 18.18% and shoulders 9.09%. Clinical features of psoriatic arthritis (PsA) are: frequently asymmetric inflammatory arthritis, affected distal interphalangeal joints (DIP), axial disease (frequently affected the cervical spine), monoarthritis, but more often oligoarthritis and other characteristics, i.e.: dactilitis, enthesitis, changes on nails and psoriasis – which might be very mild or extensive[13]. In our patients with PsA, inflammatory lower back pain had 10 patients (62.50%). Alternating gluteal pains had 7 patients (43.75%). Sacroiliitis had 6 patients (37.60%) of which bilateral (33.40%), unilateral (66.60%) patients. Sacroiliitis that leads to erosions and sclerosis in PsA is, unlike those having AS, asymmetric. Elevated ESR/CRP had 5 patients (31.25%). A positive family anamnesis had 6 patients(37.50%).Good response to NSAIDs had 9 patients (56.25%).

All patients with PsA had peripheral arthritis, i.e. 62.50% of fists and 37.50% of knees. Enthesitis was found with 5 patients (31.25%), mostly in heels (60%). One of the characteristics of arthritis in PsA is involvement of legs' finger joints, diffuse thickening of fingers (which gives a »sausage« appearance of fingers (dactilitis). Dactilitis was found in 16–48% of patients with psoriatic arthritis (PsA)[14,15]. With our patients, dactilitis was present with 6 patients (37.50%). All patients with PsA (100%) had psoriasis.

Key role in the diagnosing SpA, plays clinical presentation. Inflammatory back pain (IBP) is the most common manifestation of the disease, which is present even prior to radiological changes in SI joints, is crucial for setting up suspect on SpA. Other clinical manifestations such as peripheral arthritis, enthesitis, dactilitis and uveitis, further increase the probability of disease, and implementation of radiological techniques might confirm the existence of the disease.

Determination of HLA-B27 antigen significantly increases the likelihood of establishing an accurate diagnosis and comparing with other tests for the diagnosing SpA, has a high sensitivity and high specificity. The interaction between the MHC molecule HLA-B27 antigen with T cell response, might be the key in the pathogenesis of these clinical entities. The histocompatibility of HLA Complex which is responsible for antigen recognition, allows to distinguish own from foreign ones. An important role of the HLA molecules is to present antigenic peptides to T cells in a manner that enables appropriate T-cell receptors which interact with antigens, while simultaneously distinguishing own from foreign ones. This interaction leads to T-cell activation. HLA class I molecules generally present antigens to CD8-positive T cells, whereas HLA class II present antigens to CD4-positive T cells[16]. The results we obtained might, to a certain extent, be compared with known published data, especially when it comes to extra-spinal features of SpA.

Primary health care doctors, when using inflammatory back pain (IBP) as a parameter of making reference to a rheumatologist, might establish diagnosis of axial SpA with 1 in 7 patients. As for laboratory parameters, HLA-B27 positivity has high sensitivity and specificity (~ 90%). About 1 of 3 patients has axial SpA. Costs are higher than those for evaluating of IBP, but HLA-B27 testing takes place just once, and is therefore affordable[17].

Conclusion

Early detection, continuous monitoring of patients, as well as early implementation of biological remedies, aim to maintain as long as possible, the function of musculoskeletal system and prevent the occurrence of disability. ASAS classification criteria are important for early diagnosing SpA, but also for monitoring the performance anticytokine therapy which brings excellent results in treatment.

The most common clinical characteristics the patients of our study had were: inflammatory back pain (pain Inflammation along the lumbosacral spine), peripheral arthritis, intermittent pain in the gluteus, sacroiliitis, enthesitis, uveitis, dactilitis. This research of ours, has shown that the clinical features of HLA-B27 positive patients with SpA, in Eastern Slavonia does not differ from the clinical manifestations of patients with SpA in other parts of Europe, and which had been explicated in various different studies.

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M. Glasnović

»J. J. Strossmayer« University, Osijek University Hospital Center, Clinic for Internal Medicine, Huttlerova 4, 31000 Osijek, Croatia
e-mail: glasnovic.marija@kbo.hr

KLINIČKA OBILJEŽJA PACIJENATA SA SPONDILOARTRITISIMA I HLA-B27 POZITIVNIM ANTIGENOM

S A Ž E T A K

Cilj ovog rada bio je prikazati naša iskustva u dijagnostici spondiloartritisa (SpA) te navesti najtipičnija klinička obilježja HLA-B27 pozitivnih bolesnika. U istraživanju je uključeno 65 HLA-B 27 pozitivnih bolesnika s potvrđenom dijagnozom ankilozantnog spondilitisa (AS) i psorijatičnog artritisa (PsA) koji su tijekom 2009 i 2010 godine liječeni na Internoj klinici u Osijeku. Dijagnoza seronegativnih spondiloartritisa temeljila se na ASAS (Assessment in AS working group) klasifikacijskim kriterijima za aksijalni i periferni SpA i bila potvrđena radiološkim metodama. Za dijagnosticiranje ankilozantnog spondilitisa (AS) primijenili su se modificirani New york kriteriji. Radiološki kriterij za definitivni sakroileitis prema modificiranim New York kriterijima je bilateralni sakroiliitis stupnja 2–4 (≥2) ili unilateralni sakroiliitis stupnja 3–4. Za dijagnozu psorijatičnog artritisa (PsA) korišteni su CASPAR dijagnostički kriteriji. Ostale značajke SpA definirane su u sklopu postojećih klasifikacijskih kriterija. HLA-B27 antigen je određivan je direktnom imunofluorescentnom metodom na protočnom citometru. Prosječna starost pacijenata bila je 50,34 godina, od kojih je 27 žena (41,53%), 38 muških (58,46%). Trajanje bolesti bilo je u prosjeku 15,79 godina. U 75,38 % bolesnika postavljena je dijagnoza AS; 24.62% bolesnika imalo je dijagnozu PSA. Najčešće kliničke karakteristike koje su pacijenti imali bili su: upalna križobolja (inflamatorna bol duž lumbosakralnog dijala kralježnice), periferni artritis, naizmjenična bol u gluteusima, sakroiliitis, entezitis, uveitis, daktilitis. Ovo naše istraživanje je pokazalo da se kliničke značajke HLA B 27 pozitivnih pacijenata sa SpA u Istočnoj Slavoniji ne razlikuju od kliničkih manifestacija pacijenata sa SpA u drugim dijelovima Europe koje su iznesene u različitim studijama.