ORIGINAL ARTICLE

Association of HLA-B27 antigen with clinical and laboratory parameters in patients with juvenile idiopathic arthritis

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ABSTRACT

Aim To analyse the association of human leukocyte antigen B27 with clinical and laboratory parameters in patients with juvenile idiopathic arthritis (JIA) at the disease onset.

Methods A retrospective review of medical records of 25 HLA-B27 positive and 25 HLA-B27 negative JIA patients was performed. The diagnosis of JIA was based on the 1997-2001 International League Against Rheumatism (ILAR) criteria. Collected data: age, sex, HLA- B27 antigen presence, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid-factor (RF), antinuclear antibody (ANA), fever, rash, uveitis, enthesitis, inflamed joints and subtype of JIA.

Results HLA- B27 positive study group had more boys (p=0.01), higher erythrocyte sedimentation rate (p=0.038), higher presence of fever (p= 0.025) and enthesitis (p=0.024). Any significant difference in age of the disease onset, CRP, ANA, RF, rash, uveitis, inflamed joint and dactylitis was not noticed. The most common subtype of JIA in the HLA-B27 positive patients was ERA (60%).

Conclusion This study showed that the presence of HLA- B27 antigen plays a significant role in determining the presenting clinical and laboratory characteristics in JIA patients.-

Key words: arthritis, children, human leukocyte antigen

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common paediatric rheumatological disorder. If untreated, it could result in significant disability and even fatal outcome (1). It is defined as the presence of arthritis of unknown aetiology that begins before the age of 16 years and persists for at least 6 weeks (2). According to the International League of Associations for Rheumatology (ILAR- 2001), JIA is classified into 6 subtypes: oligoarticular (persistent or extended), polyarticular (RF-negative or RF-positive), systemic (sJIA), psoriatic arthritis, enthesitis-related arthritis (ERA) and undifferentiated arthritis (3). The main characteristic of JIA is joint inflammation with tissue destruction (4). The etiopathogenesis of the disease is still not fully understood. There is strong evidence that genetics and environmental factors (infection, stress, hormones and trauma) could result in an autoimmune reaction targeting synovial tissue (1,5). The major genetic association of different categories of JIA was found within the Human Leukocyte Antigen (HLA). It is located on the sixth chromosome, including a large group of genes involved in immune regulation (6). There is a high prevalence of the HLA-B27 allele in patients with JIA ERA (arthritis with enthesitis), similar to spondyloarthropathy (7). HLA-B27 is a class I HLA molecule that is responsible for antigen processing and presentation.

It has been proposed that HLA-B27 drives the pathogenesis of JIA-ERA by three possible mechanisms: presentation of arthritogenic peptide that causes lymphocyte activation, dimerization on the surface of antigen-presenting cells causing CD4 T lymphocyte activation, or induction of endoplasmic reticulum stress, which results in secretion of interleukin-23 and interleukin -17 (8). Occurrence of HLA-B27 antigen in children is also associated with other JIA categories, such as oligoarthritis and polyarthritis, especially among girls (9). In Bosnia and Herzegovina there are no studies that analyse effects of HLA- B27 antigen positivity in JIA patient.

The aim of this study was to analyse the association of human leukocyte antigen B27 with the clinical and laboratory parameters in patients with juvenile idiopathic arthritis (JIA) at the disease onset.

PATIENTS AND METHODS

Patients and study design

A retrospective, non-randomized clinical study was conducted at the Department of Allergology, Rheumatology and Clinical Immunology, Paediatric Clinic, Clinical Centre University of Sarajevo. The study included 50 patients who were diagnosed and treated in our Department: 25 consecutive JIA HLA-B27 negative patients and 25 consecutive JIA HLA B-27 positive patients. The period of data collection for HLA-B27 negative group was between January 2022 and July 2022, and for HLA- B27 positive group between January 2019 and July 2022. JIA diagnosis was made according to the ILAR criteria (International League Against Rheumatism) (1).

According to the presence or absence of HLA-B27, the patients were divided into two groups.

Methods

The patient data were collected from medical histories. All JIA patients underwent rheumatological clinical examination including the determination of the number and type of inflamed joint and presence of enthesitis. Arthritis was defined if at least two of the following criteria were present: inflammatory pain, limited mobility, and/or swelling. Enthesitis was specified as tenderness over the insertion site of tendon or ligaments on palpation and/or demonstrated by magnetic resonance imaging (MRI). Active sacroiliitis was defined by the presence of bone marrow oedema and contrast enhancement at the sacroiliac joint (SIJ) on MRI. Small joints included the midcarpal, carpometacarpal, metacarpophalangeal, and interphalangeal joints at the upper extremities and the talonavicular, calcaneocuboid, naviculocuneiform, tarsometatarsal, metatarsophalangeal, and interphalangeal joints of the lower extremities. Samples for HLA-B27, C- reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), rheumatoid factor (RF) typing were collected from peripheral blood. RF was considered to be positive if values were more than 15 IU/ml. HLA-B27 typing was performed using PCR- SSP kit Oleorup (UVP, Cambridge, United Kingdom) and PCR-SSO Immucor Lifecodes (Luminex Corporation, Austin, Texas,

United States of America). The presence of uveitis was diagnosed by an ophthalmologist.

Statistical analysis

The comparison of non-parametric data was performed using Mann-Whitney test as the distribution of the variables indices in the sample was non-Gaussian (according to the Shapiro-Wilks criteria). Pearson's $\chi 2$ test was used to determine the connection between qualitative characteristics. In all statistical tests $p<0.05$ was considered statistically significant.

RESULTS

The study included 50 children, 25 HLA-B27 positive and 25 HLA-B27 negative JIA patients. In the HLA-B27 positive group, boys prevailed, 16 (64%), over the girls, nine (36%) (p=0.01). In the HLA-B27 negative group there were 19 (76%) girls and six (24%) boys (p=0.01). HLA-B27 positive patients were older at the disease onset with median age of 13 years (IQ 8-14) than HLA B27 negative, median age was 7.60 years (IQ 3.6-13) (p=0.05). The two groups were largely similar in clinical presentation except for fever (p=0.025), which was found more often in patients with positive HLA-B27 (Table 1).

Table 1. Characteristics of juvenile idiopathic arthritis (JIA) patients with positive and negative HLA-B27

Variable	HLA-B27 +	HLA-B27 -	p
Mean age (min-max.) (years)	11.0±4.99 (1-17)	8.35 (5.02)	0.05
Median age (years) (IQ interquartile range)	13 (8-14.9)	7.60 (3.6-13)	0.05
Males (No, %)	16 (64.0%)	6 (24.0%)	0.01
Extra articular manifestations (No, %)			
Fever	5 (20.0)	0	0.025
Rash	5 (20.0)	4 (16.0)	0.500
Uveitis	3 (12.0)	1 (4.0)	0.300

In HLA-B27 positive patients, ANA was found positive in five (20%), rheumatoid factor in two (8%) cases but without significant difference. The analysis of erythrocyte sedimentation rate showed median value of 28 mm/h (IQ 12-37) in HLA-B 27 positive children, and median value of 16 mm/h (IQ 6-25) within HLA- B27 negative group (p=0.038). No statistically significant difference of CRP and RF between the two groups was found (Table 2).

It was shown that enthesitis was typical for JIA with HLA-B27 association (p=0.024). The data analysis showed no differences in the type of inflamed joint, presence of dactylitis, uveitis and rash in relation to the positivity of HLA-B27. Spine involvement was observed in three patients within the HLA-B27 positive group, and in two within the HLA-B27 negative group. Hip arthritis was more often diagnosed in children with HLA- B27 positivity but without statistically significant difference between the two groups (Table 3). HLA-B27 antigen was most frequently found in patients with enthesitis-related arthritis, and the HLA-B27-positive ratio was also high in polyarticular JIA, in 15 (60%) and seven (28%) cases, respectively (Table 4).

Table 2. Laboratory characteristics of juvenile idiopathic arthritis (JIA) patients with positive and negative HLA-B27

Parameter	HLA-B27+	HLA-B27-	p
CRP median (IQ range)	6.2 (1.8-23.8)	5.1 (4-16.8)	0.823
Median ESR mm (IQ range)	28 (12-37)	16 (6-25)	0.038
ANA positivity (No, %)	5 (20.0)	10 (40.0)	0.108
RF positivity (No, %)	2 (8.0)	1 (4.0)	0.500

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibody; RF, rheumatoid factor;

Table 3. Characteristics of arthritis of juvenile idiopathic arthritis (JIA) patients with positive and negative HLA-B27

Inflamed joint	No (%)of patients		p
	HLA-B27+	HLA-B27-	
Knee	18 (72.0)	18 (72.0)	0.623
Talocrular joint	11 (44.0)	16 (64.0)	0.387
Radiocarpal joint	7 (28.0)	6 (24.0)	0.500
Hip	9 (36.0)	4 (16.0)	0.098
Sacroiliac joint	5 (20.0)	1 (4.0)	0.095
Spine	3 (12.0)	2 (8.0)	0.500
Temporomandibular joint	0 (0.0)	1 (4.0)	0.500
Enthesitis	7 (28.0)	1 (4.0)	0,024
Small joints hand/feet	10 (40.0)	9 (36.0)	0.500
Dactylitis	3 (12.0)	1 (4.0)	0.269

Table 4. Subtype of juvenile idiopathic arthritis (JIA) with positive and negative HLA-B27

Subtype of JIA	No (%) of patients	
	HLA- B27+	HLA-B27-
Poliarticular form	7 (28.0)	13 (52.0)
ERA	15 (60.0)	4 (16.0)
Oligoarticular form	1 (4.0)	7 (28.0)
Psoriatic	1 (4.0)	1 (4.0)
Undifferentiated	1 (4.0)	0 (0.0)

ERA, enthesitis related arthritis;

DISCUSSION

This is the first study in Bosnia and Herzegovina analysing the correlation between HLA -B27 antigen and clinical and laboratory characteristics of paediatric patients suffering from JIA. Genetic studies are needed in order to comprehend the aetiology, pathogenesis of JIA and therapy response. Our study found a positive correlation of

male gender and HLA-B27 positivity, which was previously shown by several authors in different genetic backgrounds (9,10,11). According to the published data of Thomson et al. 76% of children with arthritis and enthesitis (ERA) have positive HLA- B27 (7); our study showed 60 %. HLA-B27 antigen is a strong risk factor for the development of enthesitis-related arthritis (12). HLA -B27 prevalence in JIA patients varies from 27.1% in Poland (10) to 21% in Nordic countries (13). Our analysis confirmed a high rate of hip arthritis (36%) in HLA- B27 positive group and a low rate of dactylitis and spine involvement. Additionally, we found that JIA patients with HLA- B27 positivity had higher ESR than the negative group, but we could not find significantly different values of CRP. At the disease onset, fever occurred more often in HLA- B27 positive group as well as the enthesitis. A study of Guo et al. did not find significant difference in fever between the two groups, although fever was described as a prime symptom in 35.6 % patients (14). Marino et al. did not find a positive correlation between HLA- B 27 positivity in JIA patients and occurrence of uveitis (15), similarly to our study. A large prospective study, which used data from Research in Arthritis in Canadian Children Emphasizing Outcomes inception cohort (ReACCh) and included 247 children, concluded that ERA patients outnumbered RF polyarticular JIA and that the rate of uveitis was 10% (16).

HLA-B27 positive individuals appear to be predisposed to excessive bone formation regardless of spondyloarthritis disease status (17). HLA-B27 is of great importance in paediatric and adult rheumatology and is subject of many ongoing studies (10). HLA-B27 positivity has been associated with worse radiographic damage, more typical marginal syndesmophytes, and more frequent syndesmophyte symmetry in spondyloarthritis (SpA) patients, where JIA-ERA can be included (18). HLA-B27 individuals appear predisposed to excessive bone formation regardless of spondyloarthritis disease status (19). Liu CH et al. studied mesenchymal stem cells (MSCs) of HLA-B27 positive SpA patients and concluded that HLA-B27 directly activates the tissue non-specific alkaline phosphatase (TNAP) pathway in syndesmophyte pathogenesis, enhance bone mineralization and ectopic bone formation at inflamed entheses (20).

JIA is a very heterogenous disease and in everyday practice there are not many clinical and laboratory markers that can serve as prognostic factors (1). HLA- B27 is known to be related to spondyloarthropathy in adults (21), but in children with JIA, HLA- B27 has a role only in disease classification. Data from Peltoniemi at al. cohort, which was a multicentric Finnish study on 167 JIA patients, showed that, after 8 years of follow-up, 41% of HLA-B27 positive patients were not in remission compared to 33% HLA-B27 negative children; furthermore, the Finnish study showed that HLA-B27 positive patients were older than HLA-B27 negative at the time of JIA diagnosis, which is in concordance with our results (22).

The main limitation of this study is the small sample size.

In conclusion, our study confirmed that HLA-B27 antigen plays an important role in determination of clinical and laboratory characteristic of JIA patients. Overall, the results obtained were only partially in accordance with the studies from other countries, which can be due to the different genetic background of the studied population. It is required to study a larger sample size and analyse the therapy response of JIA patients regarding the HLA-B27 presence.

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TRANSPARENCY DECLARATION

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