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Original Article

Human Leukocyte Antigen B27 and Juvenile Idiopathic Arthritis and Classification of Juvenile Spondyloarthropathies by the Assessment of SpondyloArthritis International Society Criteria

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Objective. We examined the clinical relationship between human leukocyte antigen B27 (HLA-B27) and juvenile idiopathic arthritis (JIA). Additionally, we assessed the usefulness of the Assessment of SpondyloArthritis International Society (ASAS) criteria for diagnosing juvenile spondyloarthropathies (SpA). **Methods.** We retrospectively reviewed medical records of 239 patients with JIA classified according to the International League of Associations for Rheumatology (ILAR) classification to analyze the features of the joint involvement site. Results were correlated with the presence of HLA-B27. After that, we classified the 239 JIA patients according to the ASAS criteria to diagnose juvenile SpA. The relationship between the ASAS criteria and a diagnosis of juvenile SpA was analyzed by a chi-squared test. **Results.** Back pain was associated with HLA-B27 in boys ($p=0.002$) but not in girls ($p=0.616$). In both sexes, involvement of the small joints in the lower extremities was highly associated with HLA-B27 ($p=0.001$ for boys, $p=0.021$ for girls). In addition, HLA-B27 was associated with enthesitis ($p=0.004$ for boys, $p=0.021$ for girls). Eighty-seven (36.4%) patients with JIA fulfilled the ASAS criteria; 2 (0.8%) had axial SpA and 85 (35.6%) had peripheral SpA. HLA-B27 was the most significant factor for diagnosing juvenile SpA (sensitivity 80%, specificity 99.31%, positive likelihood ratio, 116). **Conclusion.** The ILAR criteria have some weaknesses for diagnosing HLA-B27-positive JIA patients in early stages. The use of the ASAS criteria for juvenile patients will enable pediatric rheumatologists to diagnose juvenile SpA patients earlier. **(J Rheum Dis 2016;23:234-240)**

Key Words. Juvenile arthritis, HLA-B27 antigen, Ankylosing spondylitis, Spondylarthropathies

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease that occurs in children. It is defined as an idiopathic arthritis that persists for more than 6 weeks in patients under 16 years of age [1]. The exact causes of JIA are not well known, but it is considered that JIA is related to individual susceptibility and exposure to environmental factors [2]. Considering that JIA is a chronic form of arthritis that develops in growing children, it has variable clinical features, progression, and prognosis [3]. The symptoms at onset change during the course of the disease, making it challenging to predict progression clinically.

Many studies have reported an association between JIA and human leukocyte antigen (HLA) alleles; however, the correlation of JIA with HLA-B27 has rarely been described. It is well known that HLA-B27 is related to the manifestations of ankylosing spondylitis (AS) in adults [4]. However, the influence of HLA-B27 in children is not clear. According to epidemiologic studies, HLA-B27 is suspected to be associated with juvenile-onset spondyloarthropathy (SpA), enthesitis, and psoriasis in pediatric patients [5,6].

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SpAs are a heterogeneous group of seronegative rheumatic diseases characterized by arthritis of large peripheral joints, enthesitis, and axial disease [7]. Juvenile SpA is an HLA-B27-associated disorder that begins at 16 years of age or younger [8]. Patients with HLA-B27 can have sacroiliitis and axial diseases 5～10 years after disease onset [9-13]. These patients can show radiographic sacroiliitis on pelvic plain radiography or magnetic resonance imaging (MRI) as the disease develops. However, such radiographic change is rarely seen in children with juvenile SpA. At the time of disease onset, there are more HLA-B27-positive JIA patients without sacroiliitis or axial disease than there are patients with sacroiliitis or axial disease [14]. Therefore, among juvenile arthritis patients, there are fewer patients diagnosed with SpA than expected.

Several classification systems used for juvenile SpA include the Amor criteria [15] and European Spondyloarthropathy Study Group (ESSG) criteria [16]. The International League of Associations for Rheumatology (ILAR) classification of JIA is the most common classification system used by pediatric rheumatologists [17,18]. Juvenile SpA is involved in several subtypes of JIA (enthesitis-related, psoriatic, and undifferentiated arthritis) [19]. However, this classification system cannot include all patients with juvenile SpA. Additionally, there is a considerable number of patients with juvenile SpA who are diagnosed with other subtypes of JIA, such as oligoarticular arthritis [1,20]. This misdiagnosis occurs because the diagnosis is based on a clinical decision [19], and the symptoms of juvenile patients vary widely. The initial uncertainty and an overlapping diagnosis can lead to confusion and considerable differences in treatment and prognosis.

In this study, we retrospectively examined the clinical features related to the joint involvement in HLA-B27-positive JIA patients classified by the ILAR criteria in a cohort of patients. We identified the features specific to children with HLA-B27-positive JIA that could differentiate them from HLA-B27-negative JIA patients and predict the development of juvenile-onset SpA or adult-type AS. Later, we classified the JIA patients according to the ASAS criteria to assess the usefulness of the ASAS criteria for diagnosing juvenile SpAs.

MATERIALS AND METHODS

We conducted a retrospective, single-center study of 239 patients with JIA by reviewing their medical records during a 7-year period, between March 2006 and December 2012. Patient diagnosis was based on the ILAR criteria for JIA classification and was performed by a skilled pediatric rheumatologist after following the patients for at least 6 months. This study was approved by the Institutional Review Board at Hallym University Sacred Heart Hospital (2015-I062).

Data collection

Patient information included sex, age, and the sites of the involved joints at diagnosis and over time. The sites of involved joints were evaluated at the time of disease onset and after 5 years of observation. The following clinical SpA features were collected: inflammatory back pain, enthesitis, uveitis, dactylitis, psoriasis, and family history of SpA. Associated laboratory findings included C-reactive protein, HLA-B27, and sacroiliitis on radiographic imaging.

Definition

Hip pain was defined as pain that occurred at rest, during motion, or while applying force around the sacroiliac joints. Back pain was defined as pain on the spine occurring at rest or in motion. Enthesitis involved pain, tenderness, or swelling at the inserted sites of a tendon, ligament, or fascia. Large joints included the shoulder, elbow, and wrist of the upper extremities and the knee and ankle of the lower extremities, excluding hip joints. Small joints included the midcarpal, carpometacarpal, metacarpophalangeal, and interphalangeal joints at the upper extremities and the subtalar, talonavicular, calcaneocuboid, naviculocuneiform, tarsometatarsal, metatarsophalangeal, and interphalangeal joints of the lower extremities. Samples for HLA-B27 typing were collected from peripheral blood. HLA-B27 typing was performed with polymerase chain reaction sequence-specific primers. Imaging to determine radiographic sacroiliitis on plain radiography or MRI was performed within 5 years of disease onset.

Statistics

All statistical analyses were conducted with IBM SPSS Statistics 19.0 (IBM Co., Armonk, NY, USA). The differences in HLA-B27 expression, as categorical data, between groups were compared using the chi-squared test or Fisher's exact ratio. The Mann-Whitney U-test was used to analyze the differences in age at disease onset between sexes. The relation of variables in the ASAS criteria to juvenile SpA was analyzed by the chi-squared test. In

this analysis, p-values <0.05 were considered significant.

RESULTS

In our study, we evaluated a cohort of 239 JIA patients. The age at onset was 6.9±3.9 years (mean±standard deviation [SD]), disease duration at first visit was 9.4±13.0 months, and follow-up duration was 4.6±2.9 years. All patients were diagnosed with one of the six categories of JIA based on the ILAR criteria. Of these patients, after excluding 9 patients from analysis, 69 patients (30.0%) were HLA-B27-positive and 161 patients (70.0%) were HLA-B27-negative (Table 1). All patients with enthesitis-related arthritis were HLA-B27-positive. Other than that, the HLA-B27-positive ratio was the highest in oligoarticular persistent JIA (39.2%), followed by oligoarticular extended (36.8%), polyarticular rheumatoid factor (RF)-negative (36.0%), systemic (12.1%), and polyarticular RF-positive (6.7%) JIA. With respect to the sex distribution, the proportion of HLA-B27-positive patients was higher in boys (41.2%, 47/114) than it was in girls (19.0%, 22/116) (p=0.001, Table 2).

In boys with JIA, the age (mean±SD) at disease onset was higher in HLA-B27-positive patients (9.3±2.0 years) than it was in HLA-B27-negative patients (6.4±3.5 years, p=0.001; Table 2). In girls with JIA, the age at disease onset was 7.8±4.3 years in HLA-B27-positive patients and 5.9±4.2 years in HLA-B27-negative patients, but this difference was not statistically significant (p=0.063).

Radiographic sacroiliitis was revealed on plain radiography or MRI 5 years after disease onset in 12/69 (17.4%) HLA-B27-positive patients and 2/161 (1.2%) HLA-B27-negative patients (p=0.001, Table 2). However, the total number of patients with sacroiliitis was small compared to the total cohort.

Of the HLA-B27-positive patients, 14.9% (7/47) had back pain (p=0.002, Table 3). The ratio of enthesitis in HLA-B27-positive patients was higher than that in HLA-B27-negative patients (31.9% [15/47], p=0.004 in boys; 13.6% (3/22), p=0.021 in girls). The ratio of lower small joint pain in HLA-B27-positive patients was significantly higher than in HLA-B27-negative patients (63.8% [30/47], p=0.001 in boys; 40.9% [9/22], p=0.021 in girls). The lower large joint was the most common site of involvement in both sexes, regardless of HLA-B27 status. In HLA-B27-negative boys, the upper

Table 1. Classification performed at 5 years from disease onset in 239 children with JIA

Subgroup at onset (ILAR criteria)	Total cohort	HLA-B27 not analyzed	HLA-B27-positive	HLA-B27-negative
Systemic	63 (26.4)	5	7 (12.1)	51 (87.9)
Oligoarticular persistent	81 (33.9)	2	31 (39.2)	48 (60.8)
Oligoarticular extended	19 (7.9)	0	7 (36.8)	12 (63.2)
Polyarticular RF-negative	51 (21.3)	1	18 (36.0)	32 (64.0)
Polyarticular RF-positive	16 (6.7)	1	1 (6.7)	14 (93.3)
Psoriatic	1 (0.4)	0	0 (0)	1 (100)
Enthesitis-related	5 (2.1)	0	5 (100)	0 (0)
Unclassifiable	3 (1.3)	0	0 (0)	3 (100)
Total	239 (100)	9	69 (30.0)	161 (70.0)

Values are presented as number (%). JIA: juvenile idiopathic arthritis, ILAR: International League of Associations for Rheumatology, HLA: human leukocyte antigen, RF: rheumatoid factor.

Table 2. Sex distribution, age at disease onset and radiographic sacroiliitis in 239 children with JIA

Variable	Total	HLA-B27-positive	HLA-B27-negative	p-value
Boy:girl	117:122 (49.0:51.0)	47:22 (68.1:31.9)	67:94 (41.6:58.4)	0.001
Age (years)				
Boy	7.6±3.5	9.3±2.9	6.4±3.5	0.001
Girl	6.3±4.2	7.8±4.3	5.9±4.2	0.063
Radiographic sacroiliitis	14 (18.6)	12 (17.4)	2 (1.2)	0.001

Values are presented as number (%) or mean±standard deviation. JIA: juvenile idiopathic arthritis, HLA: human leukocyte antigen. Radiographic sacroiliitis is shown on pelvic X-ray or magnetic resonance imaging.

Table 3. Analysis of children with JIA in relation to joint involvement and HLA-B27 status

Variables	Sex	HLA-B27-positive	HLA-B27-negative	p-value
Hip pain	Boy	20/47 (42.6)	20/67 (29.9)	0.162
	Girl	2/22 (9.1)	17/94 (18.1)	0.522
Back pain	Boy	7/47 (14.9)	0/67 (0)	0.002
	Girl	2/22 (9.1)	5/94 (5.3)	0.616
Enthesitis	Boy	15/47 (31.9)	7/67 (10.4)	0.004
	Girl	3/22 (13.6)	1/94 (1.1)	0.021
Large joint of upper extremities	Boy	17/47 (36.2)	38/67 (56.7)	0.031
	Girl	14/22 (63.6)	56/94 (59.6)	0.726
Small joint of upper extremities	Boy	9/47 (19.1)	27/67 (40.3)	0.017
	Girl	8/22 (36.4)	40/94 (42.6)	0.596
Large joint of lower extremities	Boy	40/47 (85.1)	56/67 (83.6)	0.826
	Girl	22/22 (100)	77/94 (81.9)	0.040
Small joint of lower extremities	Boy	30/47 (63.8)	18/67 (26.9)	0.001
	Girl	9/22 (40.9)	16/94 (17.0)	0.021

Values are presented as number (%). JIA: juvenile idiopathic arthritis, HLA: human leukocyte antigen. Large joint: shoulder, elbow, and wrist at upper extremities; knee and ankle at lower extremities. Small joint: midcarpal, carpometacarpal, metacarpophalangeal, and interphalangeal joints at upper extremities; subtalar, talonavicular, calcaneocuboid, naviculocuneiform, tarsometatarsal, metatarsophalangeal, and interphalangeal joints at lower extremities.

Table 4. Sensitivity, specificity, PLRs and negative likelihood ratios of clinical and laboratory SpA features in patients classified according to ASAS criteria

Variable	Sensitivity (%)	Specificity (%)	PLR	NLR
Inflammatory back pain	10.47	98.69	8.01	0.91
Hip pain	29.07	77.12	1.27	0.92
Peripheral arthritis	97.67	15.03	1.15	0.15
Enthesitis	25.58	97.39	9.78	0.76
Psoriasis	1.16	100.00	ND	0.99
Uveitis	25.58	99.35	39.14	0.75
Preceding infection	2.33	99.35	3.56	0.98
Family history of SpA	1.16	99.35	1.78	0.99
CRP elevation	69.14	39.60	1.14	0.78
HLA-B27	80.00	99.31	116.00	0.20
Sacroiliitis	9.30	100.00	ND	0.91

PLR: positive likelihood ratio, SpA: spondyloarthropathy, ASAS: Assessment of SpondyloArthritis International Society, CRP: C-reactive protein, HLA: human leukocyte antigen, NLR: negative likelihood ratio, ND: not determined.

large joint was involved in 56.7% (38/67) of cases and the upper small joint in 40.3% (27/67). It was significantly higher than that among HLA-B27-positive boys (p=0.031 in upper large, p=0.017 in upper small).

According to ILAR criteria, 6 of the 239 JIA patients (2.5%) were diagnosed with juvenile SpA (enthesitis-related and psoriatic arthritis). When these patients were classified by the ASAS criteria, 87 patients (36.4%) were diagnosed with juvenile SpA (2 axial, 85 peripheral SpA). The 2 patients classified as having axial SpA have progressed to AS. Table 4 shows the sensitivities, specificities, and positive likelihood ratios (PLRs) of the various parameters that are associated with SpA. In the ASAS criteria, HLA-B27 is considered as the most significant factor for diagnosing juvenile SpA (sensitivity, 80%; specificity, 99.31%; PLR, 116). According to the chi-squared test of the related variables in the ASAS criteria, the HLA-B27-positive group were more likely to be diagnosed with SpA (odds ratio [OR]=576, p=0.001, Table 5). Inflammatory back pain (OR=8.83, p=0.001), uveitis (OR=52.25, p=0.001), peripheral arthritis (OR=7.43, p=0.002), and enthesitis (OR=12.81, p=0.001) had rel-

Table 5. Univariate analysis for clinical and laboratory SpA features in patients classified according to ASAS criteria

Variable	None (n=153)	SpA (n=86)	Odds ratio	p-value
Inflammatory back pain	2 (18.2)	9 (81.8)	8.83	0.001
Hip pain	35 (58.3)	25 (41.7)	1.38	0.289
Peripheral arthritis	130 (60.7)	84 (39.3)	7.43	0.002
Enthesitis	4 (15.4)	22 (84.6)	12.81	0.001
Psoriasis	0 (0)	1 (100)	ND	0.181
Uveitis	1 (4.3)	22 (95.7)	52.25	0.001
Preceding infection	1 (33.3)	2 (66.7)	3.62	0.265
Family history of SpA	1 (50.0)	1 (50.0)	1.79	0.678
CRP elevation	90 (61.6)	56 (38.4)	1.47	0.189
HLA-B27	1 (1.4)	68 (98.6)	576.00	0.001
Sacroiliitis	0 (0)	8 (100)	ND	0.001

Values are presented as number (%). SpA: spondyloarthropathy, ASAS: Assessment of SpondyloArthritis International Society, CRP: C-reactive protein, HLA: human leukocyte antigen, ND: not determined.

atively high diagnostic values for juvenile SpA.

DISCUSSION

The prevalence of HLA-B27 associated with JIA shows variable regional differences. In a referral center-based study of 680 patients in the USA, 14% were HLA-B27-positive and 8% of the controls carried the antigen [21]. The HLA-B27 antigen was found in approximately 16% of the population of northern Norway, Sweden, and Finland [22]. In two other population-based studies of HLA-B27 occurrence in patients with JIA, 28.6% of patients were positive for the antigen in Estonia [23] and 42% in northern Norway [24]. Among 228 patients with JIA studied in Taiwan, an HLA-B27 association was revealed in 55.2% [25]. The HLA-B27-positive ratio is lower in Japan than in Europe and the USA [26]. In our study population in Korea, the proportion of HLA-B27 positivity with JIA was 28.9%, which is relatively high.

According to a study by Boyko [27], in enthesitis-related JIA with HLA-B27, peripheral arthritis usually manifested as mono- or oligoarthritis, and the damaged joints were usually the large joints of the legs. In a study by Berntson et al. [14], HLA-B27 was described to be of increasing importance with older age at disease onset in boys with JIA, predicting highly active joints within the first 3 years of the disease, and involving small joints in the lower extremity to a greater degree than in HLA-B27-negative boys. Burgos-Vargas and Vázquez-Mellado [28] stated that the juvenile-onset AS pattern includes two distinctive features, namely enthesopathy and involvement of the tarsal region, both of which approached the discriminative value of lumbar and/or sacroiliac joint involvement throughout the 10-year follow-up.

It is well established that HLA-B27 is closely related to AS in adults [4]. In pediatric patients, HLA-B27 has been reported to be associated with juvenile-onset SpA, enthesitis-related arthritis, and psoriatic arthritis [5,6]. Some criteria can be applied to diagnose juvenile SpA, the Amor and ESSG criteria [15,16]. Additionally, the ILAR criteria, which are most commonly used by pediatric rheumatologists, categorize juvenile SpA within several subtypes: enthesitis-related, psoriatic, and undifferentiated arthritis [19]. However, the ILAR criteria do not characterize all patients with juvenile SpA. Because the symptoms of juvenile SpA are considerably variable and the diagnosis is based on a clinical decision [19], misclassification or overlapping diagnoses could occur. As a result, confusion and challenges exist in diagnosing HLA-B27-positive patients with inflammatory arthritis, so they may be categorized with various diagnoses.

Among HLA-B27-positive patients with JIA, 66%~75% actually have juvenile-onset AS or undifferentiated juvenile-onset SpA [10,29]. However, in clinical practice, the proportions are lower than expected, and most patients seem to be classified into other JIA categories, especially type II oligoarticular JIA [1,20,30]. In our cohort, of the 69 HLA-B27-positive patients, only 2 patients were diagnosed with juvenile-onset SpA and the other 2 patients were diagnosed with adult type AS at the last follow-up. Most of the HLA-B27-positive patients belonged to the oligoarticular arthritis group, with 39.2% having type I and 36.8% having type II. SpA involves peripheral arthri-

tis and enthesitis in early stages and axial disease and sacroiliitis 5～10 years after onset [9-13]. AS in adults exists as an extension of the juvenile SpA. They are not separate diseases, but instead represent diseases on the same continuum [31]. Therefore, diagnostic criteria involving both pediatric and adult patients are necessary for detecting patients who may progress to AS at an earlier stage.

Recently, several reviews have noted that the ASAS criteria for adult AS are effective for diagnosing juvenile SpA patients early [7,31]. The ASAS criteria categorize not only axial spondyloarthritis but also peripheral spondyloarthritis, which make it easier to detect juvenile patients with SpA whose manifestations primarily consist of peripheral symptoms. In our study, we found that many HLA-B27-positive patients are classified only into JIA subgroups. Therefore, we applied the ASAS criteria to the JIA patients to identify juvenile SpA patients from patients with other JIA.

HLA-B27 showed the highest values for both sensitivity and specificity (Table 4). In a univariate analysis, inflammatory back pain, radiographic sacroiliitis, HLA-B27, uveitis, peripheral arthritis, and enthesitis differentiated juvenile SpA from non-juvenile SpA (Table 5). The 2 patients with axial SpA progressed to AS during their follow-up periods. However, none of the patients with peripheral SpA has been finally diagnosed with AS, which may be because of the short follow-up period (mean 4.6 years).

The ASAS criteria seem to be useful for making an early diagnosis and preventing inappropriate treatment. An appropriate treatment started at the appropriate time would improve the quality of life of the patients. Before the generalized use of the ASAS criteria, however, further studies are needed to prove its effectiveness. Additionally, it remains controversial whether the ASAS criteria are sufficient to be applied to both juvenile and adult SpA or whether new criteria need to be developed. In our center, in the future, a prospective study is necessary over a longer follow-up period to track how many of these patients progress to definite AS.

CONCLUSION

The ILAR criteria have some weaknesses for diagnosing HLA-B27-positive JIA patients in early stages. It seems to underdiagnose many of the patients with juvenile SpA. In contrast, the ASAS criteria, developed to classify patients with axial and peripheral SpA, have some advantages for detecting juvenile SpA. The application of the ASAS criteria to juvenile patients will enable pediatric rheumatologists to diagnose juvenile SpA patients early. Treatment started during early stages will improve patient activity, comfort, and quality of life. However, before the generalized use of the ASAS criteria to pediatric patients can occur, further studies are needed.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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