HLA B27 association in children with juvenile idiopathic arthritis: a clinical study of 72 patients

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Abstract

Current studies of HLA-associations in juvenile idiopathic arthritis (JIA) are directed at detection of the hallmarks of the disease, which may significantly improve the diagnostics for JIA.

The purpose of this study was to determine the incidence of HLA B27 in children with JIA in Ukraine and to evaluate the natural history of the disease in HLA B27-positive patients.

In this study, seventy-two children with JIA were tested for HLA B27. The diagnosis of JIA was established according to the ILAR criteria, 1997-2001. HLA B27 was detected by a flow cytometry method on FACSkan using monoclonal anti-HLA B27 antibodies. The control group comprised 40 children with reactive arthritis and 17 healthy children. For the analysis of clinical data, children with JIA were divided into 2 groups. The first group consisted of 31 HLA B27-positive patients, the second of 41 children with negative HLA B27. HLA B27 was found in 43% of the children with JIA. It was observed that HLA B27-positive male patients had a significantly higher incidence of the development of JIA ($p = 0.0005$). In the presence of HLA B27 a significant association between the onset of JIA and the age of children was postulated ($p = 0.0003$). It was established that HLA B27 is a diagnostic criterion of enthesitis-related JIA ($p = 0.0000$). The patients with enthesitis-related HLA B27-positive JIA had joint damage in the form of asymmetric arthritis of the large joints ($p = 0.0006$) and enthesitis in different localizations ($p = 0.0121$). Dactilitis is a hallmark of enthesitis-related JIA with positive HLA B27 ($p = 0.0002$) and reactive HLA B27 arthritis ($p = 0.0167$).

Key words: *juvenile idiopathic arthritis, JIA, HLA B27, enthesitis-related arthritis.*

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Introduction

Current immunogenetic studies in rheumatology show that different autoimmune diseases are characterized by specific histocompatibility antigens that can be viewed as associated or pathogenetic markers of these diseases. The studies of HLA associations have proved the presence of a correlation between different histocompatibility antigens and the clinical forms of juvenile idiopathic arthritis (JIA). It has shown the heterogeneity of JIA, which was taken into consideration in the new classification of juvenile arthritis issued at the Congress of The International Antirheumatic League (ILAR) in Durban, 1997, and revised at the following congress in Edmonton, 2001. The International Society of Pediatric Rheumatologists has named juvenile idiopathic arthritis a group of chronic inflammatory diseases of the joints of unknown origin, which last for over 6 weeks in children under 16 years. The Society has distinguished seven categories of the disease [1]. In this classification of JIA (ILAR, 1997-2001), part of juvenile spondyloarthropaties (at the prespondylitic stage) is classified as enthesitis-related arthritis. Psoriatic arthritis is also placed into a separate category with its own diagnostic criteria (definition and exclusion). It is known that the presence of HLA-B27 is one of the diagnostic criteria for not only these two categories of JIA but also for juvenile spondyloarthropathies [2-4].

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Table 1. Clinical characteristics of JIA patients with positive and negative HLA B27

N		Parameter	HLA B27+	HLA B27–	p
1		number of patients, n	31	41	
2		male, n (%)	22 (71.0%)	12 (29.3%)	**0.0005**
3		mean age at the onset of disease (min-max)	13.0 (1.0-16.0)	6.0 (0.7-16.0)	**0.0003**
4		median of disease duration at the time of the study	3.2 (1.0-6.3)	4.1 (1.0-7.8)	ns
5		subtype of JIA, n (%)			
	5a	polyarthritis	3 (9.7%)	18 (43.9%)	**0.0017**
	5b	oligoarthritis, persistent	5 (16.1%)	15 (36.6%)	0.0670
	5c	oligoarthritis, extended	2 (6.5%)	3 (7.3%)	ns
	5d	enthestis-*related* arthritis	19 (61.3%)	0 (0.0%)	**0.0000**
	5e	systemic arthritis	1 (3.2%)	5 (12.2%)	ns
	5f	psoriatic arthritis	1 (3.2%)	0 (0.0%)	ns
6		characteristics of arthritis			
	6a	large joints	26	18	**0.0006**
	6b	small joints	2	0	ns
	6c	symmetric arthritis	2	23	**0.0001**
	6d	large + small joints	3	23	**0.0001**
	6e	asymmetric arthritis	26	18	**0.0006**
	6f	dactilitis	9	0	**0.0002**
7		back pain	8	0	**0.0007**
8		enthesitis	5	0	**0.0121**
9		iridocyclitis	0	2	ns
10		radiologically proven sacroileitis	2	0	ns

ns – non- significant.

This heterogenic group of HLA B27-associated inflammatory syndromes includes seronegative enthesopathy with arthropathy (SEA syndrome); juvenile ankylosing spondilitis (AS); ankylosing tarsitis; reactive arthritis (ReA); arthropathies associated with inflammatory diseases of the intestine (Crohn's disease, nonspecific ulcerating colitis) and juvenile psoriatic arthritis [3]. There are 20 subtypes of HLA B27 that have been identified to date (from HLA B27*01 to HLA B27*20). For example, it is known that HLA B27 is the most common in patients with juvenile spondyloarthropathies [5]. Other HLA antigens in different ethnic populations also play an important role in the development of juvenile ankylosing spondilitis (particularly B13, B36, DR3, CW3). Current clinical studies of HLA associations in juvenile idiopathic arthritis are focused on the detection of clinical markers for the disease, which would improve the diagnostics for JIA, and studies of immunogenetic criteria, which would determine the prognosis of the disease.

The purpose of this study was to determine the frequency of HLA B27 association in patients with JIA and to evaluate the clinical peculiarities of arthritis in HLA B27-positive patients.

Material and Methods

The study group included 72 patients with JIA (34 boys, 38 girls) with a mean age at disease onset of 9.5 years. The median disease duration at the time of the study was 3.7 years. A diagnosis of JIA was based on the 1997-2001 ILAR criteria. Clinical evaluation of the type of joint damage included the following criteria: the number and type of the joints involved (small, large or small and large joint damage); symmetry (asymmetry) of arthritis, dactilitis, enthesitis; the presence of back pain; and extraarticular changes.

In 72 children with JIA, the detection of HLA B27 was conducted by use of the flow cytometry method on

Table 2. Clinical characteristics of reactive arthritis in HLA B27 positive and negative patients

N		Parameter	HLA B 27+	HLA B 27–	p
1		number of patients, n	12	28	
2		males, n (%)	6 (50.0%)	17 (60.7%)	ns
3		mean age at the onset of disease (min-max)	13.0 (1.0-16.0)	9.5 (2.0-16.0)	ns
4		characteristics of arthritis			
	4a	large joints	9	29	ns
	4b	small joints	2	0	ns
	4c	large and small joints	0	0	ns
	4d	symmetric	0	0	ns
	4e	asymmetric	0	0	ns
	4f	dactilitis	3	0	**167**
5		back pain	0	0	ns
6		enthesitis	0	0	ns
7		iridocyclitis	0	0	ns

ns – non-significant.

FACSkan (Becton and Dickinson) with monoclonal anti-HLA B27 antibodies (Becton and Dickinson). The control group included 40 children with reactive arthritis and 17 children that were assessed for other nonrheumatic diseases.

Statistical analysis

The statistical analysis of the results of the study was conducted with "STATISTICA FOR WINDOWS 5.0" (Statsoft, USA). The comparison of parametric data was done with Mann-Whitney criteria as the distribution of the parameter indices in the samples was non-Gaussian (checked according to Shapiro-Wilks criteria). Person's criterion was used to determine the connection between qualitative characteristics (exact Fisher's criteria).

Results

The clinical characteristics of patients with JIA are presented in Table 1. Depending on the HLA B27 results, the patients were divided into 2 groups. The first group included 31 children with positive HLA B27. The second group had 41 patients with negative HLA B27. The first group included 22 (71%) boys; the second had 12 (29.3%) boys. Further studies showed that in the presence of the HLA B27 antigen male children are at significantly higher risk of developing JIA when compared with females (p = 0.0005) (Tab. 2). The mean age at the onset of the disease for the first group was 13.0 years, and for the second group was 6.0 years. It was proved that in the presence of HLA B27 the onset of the disease usually comes at puberty (p = 0.0003).

Among the patients with different clinical types of JIA, 3 (9.7%) children from the first group had polyarthritis, 5 (16.1%) – persistent oligoarthritis, 2 (6.5%) – extended oligoarthritis, 19 (61.3%) – enthesitis-related arthritis, 1 (3.2%) – systemic arthritis and 1 (3.2%) had psoriatic arthritis. In the patients from the second group, the following forms of JIA were detected: polyarthritis in 18 (43.9%) children, persistent oligoarthritis in 15 (36.6%), extended oligoarthritis in 3 (7.3%), systemic in 5 (12.2%), and there were no patients with enthesitis-related arthritis. HLA B27 was a marker for enthesitis-related arthritis (p = 0.0000). For JIA polyarthritis the important marker was the absence of HLA B27 association (p = 0.0017). A large number of children with JIA persistent oligoarthritis were HLA B27 positive (36.6%), although it did not prove to be statistically significant (p = 0.0670).

The studies conducted showed that typical joint damage in children with JIA in the presence of HLA B27 can be described as asymmetric arthritis of the large joints (p = 0.0006) with dactilitis (p = 0.0002). Symmetrical arthritis of the small joints or of the large and small joints was shown to be typical for JIA without HLA B27 association (p = 0.0001). Enthesitis was a common finding only in HLA B27-positive children (p = 0.0121).

In patients with reactive arthritis, no statistically significant correlation was found between the presence of HLA B27 and the sex, the mean onset age, or the type of joint damage (Tab. 2). Only the presence of dactilitis was a marker of reactive arthritis in the presence of HLA B27 (p = 0.0167).

The results of a comparative study of the patients with JIA, reactive arthritis, and healthy children showed that

Table 3. HLA B27 association in patients with JIA, reactive arthritis, and healthy children

	JIA	Reactive arthritis	Healthy	p_{1-2}	p_{2-3}	p_{1-3}
Number of patients	72	40	17	15	304	237
HLA B27+	31 (43.1%)	11 (27.5%)	2 (11.8%)			

HLA B27 association with JIA is statistically significant ($p = 0.0237$) (Tab. 3).

Discussion

The first reports on the association of the MHC class I gene, HLA B27, were published in 1973 for a group of older children with pauciarticular JIA [6]. In the 1980s, Jacobs et al. and Hall et al. reported HLA B27 to be associated with spondyloarthritis and enthesitis in childhood arthritis. The majority of those children were boys, the arthritis involved mainly large joints in the legs, ethesopathy and acute iritis were common. HLA B27 was shown to be associated with the development of sacroiliitis 3-10 years after the onset of the disease [7, 8].

According to Zholobova [9], the distribution of HLA B27 in the general population in Russia constitutes approximately 10% [9]. Hence, the results of this study on the distribution of HLA B27 in the healthy (control) group in Ukraine (11.8%) correspond with previously reported data.

The frequency of HLA B27 association in Ukrainian children with JIA was found to be high – 43.1%. Among 228 patients with juvenile idiopathic arthritis studied in Taiwan, HLA B27 association was revealed in 55.2% [10]. Similar results on the frequency of HLA B27 have been published for groups of patients in Thailand, Korea, and Norway, whereas a low rate of HLA B27 positivity was found in Japan [11-15]. Moe and Rygg suggest that the high proportion of HLA B27 in the JIA population is related to a high prevalence of HLA B27 in the general population [13]. The HLA B27 antigen was found in roughly 16% of the population of Northern Norway, Sweden, and Finland. In two other population-based studies of HLA B27 occurrence in patients with JIA, 28.6% of patients had positive antigen studies in Estonia and 42% in Northern Norway [16, 17]. 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 [18]. It is also interesting that the highest incidence of JIA was reported earlier in Northern Norway where the prevalence of HLA B27 in the general population is high, as is the incidence of AS in adults [19].

Even though the detection of a phenotype cannot be the single diagnostic criterion for JIA, these studies do help to establish a preliminary diagnosis. It was proved in 100% of the cases that the detection of HLA B27 is a marker for the enthesitis-*related* type of JIA. According to the data in other studies conducted by Packham and Bowness [20] the frequency of HLA B27 in enthesitis-*related* arthritis is nearly 70% [20].

In this present study, enthesitis-related arthritis was diagnosed in 61.3% of children with a positive HLA B27 marker, and in 26.4% of all the patients with JIA. According to Children's Rheumatology Clinic in Garmisch-Partenkirchen, Germany, nearly 30% of all the children with JIA meet the criteria for enthesitis-*related* arthritis [21].

There have been three large reviews in the literature with an analysis of the natural history of enthesitis-related arthritis [22-24]. The number of patients included in the two studies [22, 24] was 84 and 55 respectively. Analysis of the data shows a prevalence of males among the patients with enthesitis-*related* JIA: 73 boys out of 84 patients, 11 boys out of 12 patients, and 17 boys out of 19 patients in this study. The mean onset age in the two studies was 10.5 and 12 ± 2.5 years respectively, which corresponds with the results of the present study – a mean onset age for enthesitis-*related* arthritis – 13.0 years [22, 23].

Asymmetric arthritis of the large joints was diagnosed in 26 HLA B27-positive patients with JIA, who were included in this study. Mostly, these were patients with enthesitis-*related* arthritis (19 children), persistent oligoarthritis (5 children) and extended oligoarthritis (2 children). Asymmetrical oligoarthritis was detected in 15 patients with persistent oligoarthritis and in 3 patients with extended oligoarthritis who had negative HLA B27.

The patients with enthesitis-*related* juvenile arthritis with HLA B27 association are mostly teenaged boys with clinical signs of asymmetric mono- and oligoarthritis of the large joints. In this study, peripheral arthritis usually manifested as mono- or oligoarthritis. The damaged joints were usually the large joints of the legs. At the onset of the disease the knee and ankle joints were damaged the most often (> 70%). In one boy arthritis of the right sterno-clavicular joint was found and proved histologically. In some cases joint damage was observed, especially the hip joint.

In this study, enthesitis was detected only in patients with enthesitis-*related* JIA. In the study of Li et al., 2003, enthesitis was described in 9 out of 12 children with enthesitis-related arthritis [23]. Wahn et al., 2001, say that 50% of patients with enthesits-related JIA have enthesitis [21]. Leblanc [22], talks about the localization of enthesitis in the patients: the femoral-suprapatellar joint – 17%, the Achilles tendon – 18%, the

plantar – 23%, enthesitis having been found in 5 out of 19 children studied (26.3%) [22].

Another typical feature of enthesitis-related arthritis is dactilitis, found in 9 out of 19 patients in current study (47.4%). According to Leblanc [22], dactilitis was found in 15 % of patients, and according to observations conducted by Hafner, dactilitis was found in every third child [22]. Long-term studies conducted for children with enthesitis-*related* JIA show that half of them develop sacroileitis in the future [20, 25]. Therefore, when conducting a clinical assessment, special attention should be paid to complaints of back pain and any changes which are typical of sacroiliitis that show on X-rays. Back pain was present in 8 out of 19 of children with enthesitis-*related* JIA but only 2 of them had radiological signs of sacroiliitis (10.5%). According to Leblanc et al., the back pain was present in 13-17% of patients [12]. Flato et al. report radiologically proven sacroileitis in 35% of children with enthesitis-related JIA [24].

Although data reported in the literature shows that 10% to 15% of patients with enthesitis-*related* arthritis develop uveitis, we did not have any patients with enthesitis-*related* arthritis who experienced any ophthalmological changes [21].

Conclusions

1. HLA B27 was positive in 43% of the studied patients with JIA.
2. In the presence of HLA B27, boys are at higher risk of developing JIA than girls (p = 0.0005).
3. In the presence of HLA B27 children at puberty (a mean onset age of 13.0 years) have a higher incidence of JIA (p = 0.0003).
4. HLA B27 is an important diagnostic criterion of enthesitis-*related* arthritis (p = 0, 0000). Asymmetric arthritis of the large joints and enthesitis is a clinical feature of enthesitis-related JIA with positive HLA B27 (p = 0.0006; p = 0.0121).
5. Dactilitis is a diagnostic marker for enthestis-*related* JIA with positive HLA B27 (p = 0.0002) and reactive arthritis with positive HLA B27 (p = 0.0167).

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