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Clinical Science

Analysis of Clinical Symptoms and Laboratory Profiles in Children with Juvenile Idiopathic Arthritis in Malopolska Region (Poland) in the Years 2007-2010

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Key words: juvenile idiopathic arthritis; epidemiology; HLA-B27; uveitis; rheumatic factor.

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Abstract

Background: Juvenile idiopathic arthritis (JIA) is a heterogenic group of chronic inflammatory connective tissue diseases of unknown aetiology in children up to 16 years of age.

Aim: The aim of this study was to analyse the incidence, clinical presentation and laboratory findings in children with JIA in Malopolska region.

Materials and methods: A retrospective analysis included all children with JIA (N=251) hospitalized in the two reference rheumatology centres covering Malopolska region (Poland), between July 2007 and December 2010.

Results: The annual incidence of JIA in Malopolska region was estimated at 9.5 per 100 000 children. Oligoarthritis (54.9%) was the most common category in all age groups with a tendency to decrease with age; from 71.4 % in children aged 1-6 years; 55.7% in aged 7-12 years to 39.3 % in aged 13-16 years. The frequency of polyarthritis and enthesitis-related arthritis was greater in adolescents (29.2 % and 22.5 %, respectively). HLA-B27 antigen and uveitis were most frequently found in children with enthesitis-related arthritis (58% and 18.5 %, respectively).

Conclusions: The study suggests the improvement of diagnostic capacity of JIA during the last decade in Poland. In accordance with the existing data diverse clinical presentation of JIA categories and laboratory characteristics were proven.

Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory arthropathy in developmental age. It represents a heterogeneous group of diseases of unknown aetiology characterized by the onset of symptoms of arthritis before the age of 16 years, lasting for more than 6 weeks [1]. The current classification system by International League Against Rheumatism - ILAR (Edmonton 2001) distinguish seven JIA categories, characterized by different clinical presentation and laboratory findings, as well as the outcome [1]. The annual incidence of JIA is estimated at 2 to 20 cases per 100 000 children, with a prevalence of 16 to 150 cases per 100 000 children worldwide, with no clear racial predilection [2]. In Poland, a decade ago, the incidence was estimated at 5 - 6.5 per 100 000 children, with almost twice higher numbers in girls (1.5-2:1), on the basis of data from Lodz and Kielce regions [3,4].

The aim of this study was to analyse the

incidence, clinical presentation and laboratory findings in children with JIA in Malopolska region.

Material and Methods

The retrospective analysis enrolled all children diagnosed with JIA in two reference rheumatology centres (Department of Paediatrics, Rheumatology and Environmental Diseases and Department of Older Children with subunits of Neurology, Rheumatology and Rehabilitation) covering Malopolska region between 1st of July 2007 and 31st of December 2010.

The study included all patients who met the diagnostic criteria of JIA by ILAR revised in 2001 (age less than 16 years, the duration of symptoms of arthritis for more than 6 weeks, exclusion of other causes of arthritis) [1]. The analysis excluded children diagnosed with infectious, reactive, toxic and allergic arthritis, proliferative diseases, and other inflammatory connective tissue diseases, arthropathies in haematological, immune and metabolic diseases, systemic non-inflammatory connective tissue diseases, psychogenic rheumatism (pain syndrome) and fibromyalgia. According to the current classification system seven categories of JIA were distinguished [1].

The analysis included the following clinical data retrieved from medical records: articular changes at the beginning of the disease, age of onset, duration of symptoms of arthritis (swollen joints) at the time of diagnosis (scored as patient referral to the reference rheumatology centre), auxological parameters, ocular changes, the therapy applied, and verification of the diagnosis after six months of illness, as well as laboratory tests results (erythrocytes sedimentation rate and serum levels of C-reactive protein at the admission to the referral centre, and the presence of antinuclear antibodies, anti-cyclic citrullinated peptide antibodies, rheumatoid factor, antigen HLA B27 detected during 6 months follow-up).

All patients were followed for at least 6 months. Those with active disease are followed by the centers until adulthood. The study was approved by the Bioethics Committee in Cracow.

Laboratory assessments were performed in certified laboratories. Reference values for C-reactive protein (CRP) was <10 mg/L, for anti-cyclic citrullinated peptide antibodies (anti-CCP) <5 RU/mL, and for rheumatoid factor (RF) <10.8 IU/mL.

Antinuclear antibodies titre was measured by indirect immunofluorescence method followed by immunodiffusion (ImmunoBlott profil Euroline 3, Euroimmun, Poland). RF rheumatoid factor IgM were determined twice at an interval of 12 weeks, semi-quantitatively by Waaler-Rose Test. Anti-CCP was assessed by ELISA kit from Euroimmun Polska (Wroclaw, Poland). Human leukocyte antigen B27 (HLA-B27) was determined in peripheral lymphocytes by serotyping.

Statistical analysis

Statistical analyses were performed using the STATISTICA 10.0 PL for Windows software package (StatSoft Polska, Kraków, Poland) and MedCalc 12.3.0.0. (Mariakerke, Belgium). Values are presented as means and 95% confidence intervals or medians with interquartile ranges. For comparison of groups, we used the chi^2 test and chi^2 test for trend (qualitative variables) and ANOVA, followed by Tukey's test or ANOVA Kruskal-Wallis (quantitative variables). In all statistical tests the 'p' values below 0.05 were considered statistically significant.

Results

Patients characteristics'

Two-hundred-fifty-one children, all Caucasians, were diagnosed with JIA between 1st of July 2007 and 31st of December 2010. There were 138 girls and 114 boys (ratio 1.2:1) in age from 1 to 16 years (mean 9.5 year at the time of diagnosis). There was no patient excluded from the analysis.

Table 1: Jjuvenile idiopathic arthritis (JIA) categories in analyzed population of Maloposka region.

JIA categories	Study population [N=251]
	N (%)
Systemic arthritis	22 (8.8)
Oligoarthritis	138 (54.9)
Persistent course	130 (51.7)
Extended course	8 (3.2)
Uniarticular onset*	87 (35.0)
Polyarthritis, rheumatoid factor positive	9 (3.6)
Polyarthritis, rheumatoid factor negative	48 (19.1)
Enthesitis-related arthritis	27 (10.8)
Psoriatic arthritis	4 (1.6)
Unclassified	3 (1.2)

* category not included in ILAR classification.

On the basis of the obtain data the annually incidence of JIA was estimated at 9.5 per 100 000 children in Malopolska region, Poland (for the paediatric population of 758 213 – average value in years 2008-2010).

JIA categories

The incidence of JIA subtypes were shown in Table 1. The mean age of symptoms onset (arthritis) of JIA subtypes was significantly different (Table 2). Children with polyarthritis and enthesitis-related arthritis were significantly older than those with oligoarthritis (in 78% affecting the knee).

The relationship between age and diagnosed JIA categories is better illustrated by Figure 1, with the

Table 2: Clinical and laboratory characteristics of the individual types of juvenile idiopathic arthritis. Data shown at mean values and 95% CI or median with interquartile range†. (NA – non applicable)

	Systemic onset [N=22]	Oligoarticular onset [N=138]	Polyarticular onset [N=57]	Enthesitis-related arthritis [N=27]	Juvenile psoriatic arthritis [N=4]	Unclassified course [N=4]	ANOVA p
Gender [f/m, ratio]	11 / 11 1:1	81 / 57 1.4:1	35 / 22 1.6:1	8/ 19^^ 1:2.4	1 / 3 -	1 / 2 -	NA
Age of JIA onset [years] †	7.7 (3.5 – 13.0)	7.8 (3.3 – 12.1)	11.1^ (7.3 – 14.0)	13.7^^^ (11.9 – 15.5)	10.0 (9.5 – 10.3)	11.6 (10.9 – 13.0)	<0.001
Duration of JIA symptoms at the time of diagnosis [months] †	1.2**# (0.1 – 2.4)	3.0 (1.2 – 5.0)	3.0 (1.8 – 6.0)	6.0* (3.0 – 9.6)	6.0 (1.2 – 12.0)	5.2 (3.0 – 6.9)	0.005
Uveitis [number, (%)]	1 (4.5)	5 (3.6)	3 (5.3)	5 (18.5)	0	0	NA
Sedimentation rate at admission [mm/h]	87*** (73 – 100)	29 (24 – 33)	39 (30 – 48)	24 (15 – 33)	38 (0 – 128)	35 (0 – 100)	<0.001
SR >12 mm/h at admission [number, (%)]	22 (100)^^^	85 (61.6)	47 (82.5)^^	13 (48.2)	2 (50)	2 (66.6)	NA
CRP at admission [mg/l]	105.7*** (55.8 – 155.6)	10.3 (7.3 – 13.3)	20.1 (14.2 – 26.1)	10.0 (4.6 – 15.3)	12.6 (0 – 39.1)	11.5 (0 – 26.8)	<0.001
CRP > 10 mg/l at admission [number, (%)]	21 (95.5)***	31 (22.3)	30 (52.6)^^^	8 (30.8)	1 (25)	2 (66.6)	NA
Rheumatoid factor [number of seropositive, (%)]	0	1 (0.7)	9 (15.8)	0	0	0	NA
Anti-nuclear antibodies [number of seropositive/tested, (%)]	2/22 (9.1)	53/131 (40.5)	17/56 (30.4)	7/25 (28)	1/4 (25)	1/4 (25)	NA
HLA-B27 [number/tested, %]	1/13 (7.7)	24/103 (23.3)	12/37 (32.4)	15/26 (57.7)	1/4 (25)	0/4	NA

^^^p<0.001, ^^p<0.01 ^p<0.05 vs. oligoarticular onset; #p<0.001 vs. enthesitis-related arthritis; ***p<0.001, **p<0.01; *p<0.05 vs. oligoarticular onset as well as polyarticular onset.

presentation of prevalence in age clusters. There is a clear, statistically significant, dominance of oligoarthritis among the youngest patients (71.4 % in the 1-6 years old subgroup) with a tendency to decrease with age (39.3 % in the 13-16 years old subgroup). On the contrary, enthesitis-related arthritis became more frequent in the oldest group.

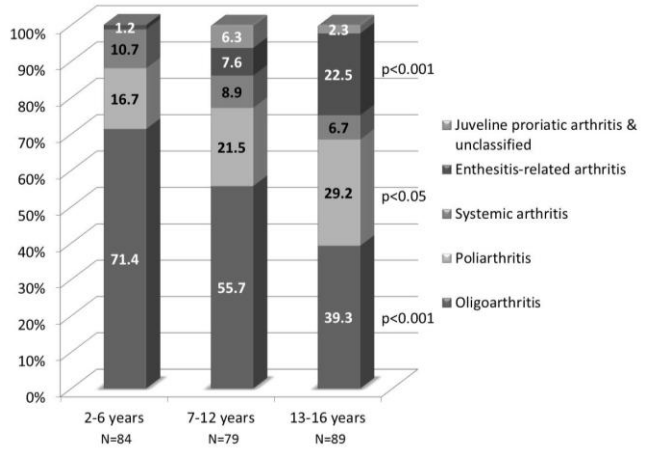

Figure 1: The incidence of the individual categories of juvenile idiopathic arthritis in age groups. P-values for chi^2 for trend in subsequent age categories for the incidence of oligoarthritis, polyarthritis and enthesitis-related arthritis.

The duration of symptoms established before the diagnosis was presented in the Table 2. Patients with systemic arthritis had the shortest history of symptoms at the time of diagnosis (median value 1.2 months; $p < 0.05$), which is the consequence of acute clinical presentation resulting in the immediate hospitalization. It took much longer to diagnose children with enthesitis-related arthritis - 6 months in average. They were frequently initially misdiagnosed as avascular necrosis or degenerative disc disease.

Laboratory findings

Analysis of markers of inflammation (CRP, ESR) at the admission to the referral centre, revealed a statistically significant increase in the ESR in subgroup with systemic arthritis, than in the patients with oligoarthritis and polyarthritis. Increased values of ESR and CRP (ESR > 12 mm/h; CRP > 10 mg/l) were shown in 100% and 95.5% of children with systemic arthritis, respectively. Higher levels of inflammatory markers at the referral were also showed in patients with polyarthritis than oligoarthritis (Table 2).

Rheumatic factor (RF) and anti-CCP

The frequency of patients seropositive for RF (assessed in all patients) is presented in Table 2. Anti-CCP antibodies were assessed in 101 patients, mostly in those with polyarthritis (N=29) and oligoarthritis (N=50).

There were 9 patients (8 females) RF seropositive (15.8%), including 6 seropositive and 3 seronegative for anti-CCP among children with oligoarthritis. Additionally, in one RF seronegative patient with oligoarthritis anti-CCP antibodies were detected.

Antinuclear antibodies (ANA)

The presence of ANA (in titter > 1:160) were found in 81 patients out of 241 tested (32.3% of cases), most frequently in those with oligoarthritis (40.5% of all; 44.9% of females and 34% of males). ANA were also frequently detected in patients with polyarthritis (30.4%) and enthesitis-related arthritis (28%) – Table 2.

HLA B27

The antigen HLA B27 was found in 53 of 186 tested patients - 28.5% (Table 2). Most frequently HLA-B27 antigen was present in patients with enthesitis-related arthritis – 57.7%, polyarthritis - 32.4%, and oligoarthritis – 23.3%. On the bases of the 5.3% prevalence of HLA-B27 among 400 blood donors in Poland [5], we estimated odds ratios (OR) for JIA subtypes at: 24.6 (95% CI 10.1 - 60.1) for enthesitis-related arthritis, 8.7 (3.8 - 19.6) for polyarthritis and 5.5 (2.9 - 10.3) for oligoarthritis.

Uveitis

Ophthalmological examination was performed in all of the 251 analysed patients. Fourteen patients were diagnosed with uveitis (5.6% of the study group). This symptom was observed usually in patients with oligoarthritis and enthesitis-related arthritis (Table 2). 14.3% of children with uveitis were seropositive for ANA, and 64.3% had HLA-B27 antigen. Patients with uveitis and HLA-B27 antigen were older (median age of JIA onset 13.5 yrs.) than ANA-seropositive patients without HLA-B27 antigen (median age of JIA onset 5.4 yrs.).

Seasonality of JIA

The result of the seasonal incidence of JIA cases in the Malopolska population is presented in Figure 2. The onset of oligoarthritis occurred most frequently in spring and autumn, while less frequently during winter and summer (the differences were not statistically significant). No seasonality was demonstrated for enthesitis-related arthritis.

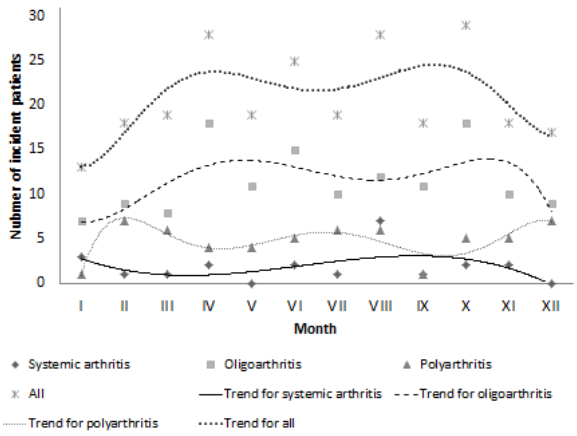

Figure 2: Seasonality of incidence of JIA categories.

Discussion

Our study estimated the current incidence of JIA at 9.5 per 100 000 children, almost 2-fold greater than has been shown about a decade ago for the region of Lodz and Kielce (5-6.5 per 100 000) [3, 4]. The obtained data suggest rather the improvement in the diagnostic capacity of JIA in our country, than the increasing incidence of the disease.

Numbers reported by us are slightly lower than in Nordic countries - 15 per 100 000 children/year [6], but greater than in Alsace (France) - 3.2 per 100 000/year in children under age 16 years [7].

The structure of the subtypes of JIA is almost in line with the register of British Paediatric Rheumatology Group. Only the incidence of juvenile psoriatic arthritis was lower (1.6% *vs.* 7.0%). The lack of inclusion of unclassified arthritis in BRRG register cannot explain the difference [8, 9]. The lower prevalence of juvenile psoriatic arthritis in our group of patients could be explained by heterogeneous clinical feature of this entity [10], also influenced by the applied therapy, that might cause its misclassification as other JIA category.

Oligoarthritis accounted for about 40%of JIA cases in France [7], 50% in United Kingdom [8,9] and 54% in Estonia [11]. Not only in European countries but also in other continents, oligoarthritis is the most common JIA category among Caucasians [12].

Our data confirm the differences in the clinical and laboratory characteristics of JIA categories, which do not have in many aspects, a counterpart in adulthood, and still rising controversies, being a subject of debate on the revision of the nomenclature and classification of JIA [13].

The clinical and laboratory characteristics of JIA patients with systemic arthritis showed gender equality (ratio 1:1) typical for this entity, high levels of inflammatory markers, and the presence of ANA only in a small subset of patients (9%). The diversity of this category is probably due to the autoimmune pathogenesis, that is a key element in the discussion concerning the necessity of revision of the current JIA classification and its separation as individual entity, the equivalent of Still's disease in adults. It is worth noting that originally, JIA with the systemic onset was named Still’s disease.

The most common category of JIA in our study was oligoarthritis, diagnosed in 54.9 % of children, 1.4-time more frequent in girls. Initially, the disease frequently involves single large joint: knee, ankle, elbow, wrist. It was also true for our population. The uniarticular symptomatology was presented by 63% of patients, usually affecting the knee (78%). The laboratory profile confirmed relatively low severity of inflammatory reaction at the initial presentation. 38% were ANA seropositive, more predominantly girls (1.9:1). We showed increased frequency of HLA-B27 (23.3 %) in this category and uveitis in 4% of patients. As it is well known, the clinical course of oligoarthritis is heterogeneous. In some cases the disease is

evolving to rheumatoid arthritis (RF seropositive and more frequently seronegative), while in the other patients is leading to inflammatory spondylo-arthropathy with initial peripheral manifestation.

Another analysed JIA category – polyarthritis, diagnosed in 22.7% of patients, included mostly RF seronegative cases (84%). RF seropositive disease occurs usually in adolescents, presents with erosive changes and bone deformities, and corresponds to rheumatoid arthritis in adults. In this subgroup 52.6% patients had increased CRP and 82.5% ESR at admission to the reference centre. Almost one third of patients were seropositive for ANA, and HLA B27 antigen was found in 32.4% of affected, 8 times more frequently than in the general population.

Enthesitis-related arthritis accounted for 10.8% of all JIA cases, and as expected was 2.4 times more often among boys, mostly adolescents, with frequent prevalence of HLA B27 antigen (in 58% of patients). It can be estimated that HLA B27 antigen is increasing the risk for development of enthesitis-related arthritis by 25 times. Additionally, in 18.5% of patients uveitis was diagnosed. The subgroup with enthesitis-related arthritis was characterized by the longest history of symptoms at the time accurate diagnosis was established - 6 months in average. Initially, due to nonspecific tendon pain, the patients are frequently misdiagnosed with avascular necrosis or degenerative disc disease. The disease affects, in addition to the Achilles tendon and plantar aponeurosis, attachment of patellar ligament at the tibial tuberosity, and attachments of deep back muscles. The family history of HLA B27 related disease, peripheral joint involvement, and the presence of the antigen shorten the period to the accurate diagnosis.

Juvenile psoriatic arthritis was a sparse category of JIA in the study population (1.4%). Even such a small group (3 boys and 1 girl) had typical for this category characteristics - later onset (median age of 10 years), low intensity of inflammation, the absence of RF and anti-CCP antibodies.

This study shows that the JIA population of children in Malopolska region has similar clinical presentation and laboratory profile as observed in other European affected populations [2, 9]. The delay in the proper diagnosis and initiation of adequate therapy in children with the other JIA categories than systemic arthritis, still rising concern. The time to diagnosis needs to be shorten below 6 months by increasing public awareness, especially in rural areas, as well as the knowledge of paediatricians. Only early referral of patients with symptoms of JIA to rheumatologists and not to orthopaedists (despite the absence of a history of trauma) may improve the current situation.

An interesting finding presented in the study is the seasonality of JIA. The strongest seasonality of the incidence was found in the group of children suffering from oligoarthritis. The lower incidence of JIA was reported in winter and summer months. The increase in the occurrence in spring and autumn overlap with the peak incidence of infections, and is in line with hypotheses emphasising the role of infectious factors as triggering mechanism in predisposed individuals. As the analysis was underpowered and based on self-reported data, a potential bias cannot be excluded. Small children report the onset of symptoms not very accurately, while parents frequently wrongly interpret children's complains and seek medical advice with a delay.

Our study has some limitations. The incidence of JIA may be underestimated, as we could not exclude that some children living in the distant sites in the region were refereed to neighbouring regions. In our opinion the number of such cases was low, if any.

Conclusions: The study suggests the improvement of diagnostic capacity of JIA during the last decade in Poland. In accordance with the existing data diverse clinical presentation of JIA categories and laboratory characteristics were proven.

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References

1. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31:390–2.

2. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet. 2007;369:767-78.

3. Wolny-Niedzielska A. [Diseases of the musculoskeletal system in children referred to the Rheumatology Clinic in Kielce in 1999-2003]. Reumatologia. 2005;43:265–73.

4. Zygmunt A, Biernacka-Zielinska M, Brózik H, et al. [Rheumatic diseases in the population of children and young people from the region of Łódź]. Ped Pol. 2005;80: 995–1001.

5. Musiej-Nowakowska E, Mączyńska-Rusiniak B, Kołodziejczyk B, Gazda A. [HLA-B27 and HLA-DR: prognostic factors in systemic onset juvenile idiopathic arthritis]. Reumatologia. 2011;49:23–31.

6. Berntson L, Andersson Gäre B, Fasth A, et al. Incidence of juvenile idiopathic arthritis in the Nordic countries. A population based study with special reference to the validity of the ILAR and EULAR criteria. J Rheumatol. 2003;30:2275-82.

7. Danner S, Sordet C, Terzic J, et al. Epidemiology of juvenile idiopathic arthritis in Alsace, France. J Rheumatol. 2006;33:1377-81.

8. Symmons D, Jones M, Osbourne J, et al. National Diagnostic Index: Paediatric Rheumatology in the United Kingdom (1996). Data from the British Paediatric Rheumatology Group National Diagnostic Register. J Rheumatol. 1996;23:1975–80.

9. Packham JC, Hall MA. Long-term follow-up of 246 adults with

juvenile idiopathic arthritis: functional outcome. Rheumatology (Oxford). 2002;41:1428-35.

10. Butbul Aviel Y, Tyrrell P, Schneider R, et al. Juvenile Psoriatic Arthritis (JPsA): juvenile arthritis with psoriasis? Pediatr Rheumatol Online J. 2013;11:11.

11. Pruunsild C, Uibo K, Liivamägi H, et al. Incidence of juvenile idiopathic arthritis in children in Estonia: a prospective population-based study. Scand J Rheumatol. 2007; 36:7-13.

12. Saurenmann RK, Rose JB, Tyrrell P, et al. Epidemiology of juvenile idiopathic arthritis in a multiethnic cohort: ethnicity as a risk factor. Arthritis Rheum. 2007;56:1974-84.

13. Martini A. It is time to rethink juvenile idiopathic arthritis classification and nomenclature. Ann Rheum Dis. 2012;71:1437-9.