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Research Article

Juvenile Idiopathic Arthritis in Adults: Long-Term Observation of Ukrainian Patients

Marta Dzhus

Abstract
The assessment of long-term outcome of functional disability and disease activeness in adult patients with juvenile idiopathic arthritis appears to be complicated due to the absence of a unified approach to the classification and estimation of disease activeness, as well as the loss of supervision over a patient because of remission or his/her transition from pediatric to adult rheumatic service.
The objective of the research was to determine how adults with the history of juvenile idiopathic arthritis fulfill the classification criteria for adult rheumatic diseases, as well as to assess activeness of these diseases, the degree of functional disorders, and social activeness of patients in Ukraine.
Materials and methods. Patients with juvenile idiopathic arthritis older than 18 years and with more than 3 years of disease duration living in different parts of Ukraine were included into the study. Data regarding sociodemographic features, fulfillment of adult classification criteria, Health Assessment Questionnaire, articular and extra-articular Juvenile Arthritis Damage Index and disease activity were analyzed.
Results. We observed 122 adult patients with the history of juvenile idiopathic arthritis irrespective of the presence of active inflammation at the moment of the examination. This group included patients from different regions of Ukraine diagnosed with juvenile idiopathic arthritis during 1984-2013. An adult rheumatologist examined all patients and the diagnosis was revised according to the adult classification of rheumatic diseases. Typical diagnostic criteria for rheumatoid arthritis were estimated in 32.8% of patients, ankylosing spondylitis – in 31.1% of patients, undifferentiated arthritis – in 13.9% of patients, Still's disease – in 4.9% of patients, psoriatic arthritis – in 0.8% of patients, steady clinical laboratory remission – in 16.5% of patients. Most patients (81.8%) with rheumatoid factor positive polyarticular juvenile idiopathic arthritis fell under rheumatoid arthritis criteria in adulthood, and in 85% of patients with enthesitis-related arthritis as well as 53.8% of patients with extended oligoarthritis ankylosing spondylitis developed in adulthood. 68.8% of patients with systemic juvenile idiopathic arthritis, 68% of patients with rheumatoid factor negative polyarthritic subtype and 55% of patients with enthesitis-related arthritis had disability and incapacitation. Minimal disorders of the patients' general condition according to the Health Assessment Questionnaire in adult age were found in most subtypes of juvenile idiopathic arthritis classified according to the International League of Associations for Rheumatology (extended and persistent oligoarthritis, rheumatoid factor positive polyarthritis, systemic subtype); moderate disorders of the general condition were found in enthesitis-related arthritis and rheumatoid factor negative polyarthritis. Side effects of juvenile idiopathic arthritis according to the articular Juvenile Arthritis Damage Index included severe articular damage being most frequently found in systemic and rheumatoid factor positive polyarthritis subtypes of juvenile idiopathic arthritis, while side effects of juvenile idiopathic arthritis according to the extra-articular Juvenile Arthritis Damage Index included extra-articular damage being found in systemic and rheumatoid factor negative polyarthritis subtypes of juvenile idiopathic arthritis, that was confirmed by the assessment of physical health according to the Short Form Health Survey-36, which was the worst in patients with systemic (40.3 ± 12.6) and rheumatoid factor negative polyarthritis (38.9 ± 9.4) subtypes of juvenile idiopathic arthritis.
Conclusions. Further research of remote consequences of juvenile idiopathic arthritis in adult age and long-term observation of such patients require a detailed study to improve diagnostics and provide adequate treatment of rheumatic diseases with juvenile onset in adult age.

Keywords
adult juvenile idiopathic arthritis, outcome, transformation

O.O. Bohomolets National Medical University, Kyiv, Ukraine
*__Corresponding author__: dzhusm@yahoo.co.uk

Problem statement and analysis of the recent research

The assessment of long-term outcome of functional disability and disease activeness in adult patients with juvenile idiopathic arthritis (JIA) appears to be complicated due to the absence of a unified approach to the classification and estimation of disease activeness, as well as the loss of supervision over a patient because of remission or his/her transition from pediatric to adult rheumatic service. All these facts lead to

insufficient understanding of JIA clinical presentations by adult rheumatologists. According to many registers (Portugal, Germany), up to 56% of patients after reaching 18 years of age continue to be observed by adult rheumatologists due to an active disease [1, 2]. In such patients, the diagnosis is often changed according to adult rheumatology terminology. In 2016, Olivier-Ramos et al. [3] published their observations of adult patients who were included into the Portuguese register of patients with juvenile diseases; the researchers examined symptoms of JIA in childhood and their transformation into various diseases in adult age. It was the first publication focusing on how patients with JIA fulfill the classification criteria for adult rheumatic diseases. There is a lack of information about the social status (including study, professional activeness, disablement) of adults with JIA.

Thus, the objective of the research was to determine how adults with the history of JIA fulfill the classification criteria for adult rheumatic diseases as well as to assess activeness of these diseases, the degree of functional disorders, and social activeness of patients in Ukraine.

1. Materials and methods

We observed 122 adult patients with the history of JIA irrespective of the presence of active inflammation at the moment of the examination. This group included patients from different regions of Ukraine diagnosed with JIA during 1984-2013. Inclusion criteria were: patients with JIA according to the 2001 revised International League of Associations for Rheumatology (ILAR) criteria [4], who at the time of data analysis were older than 18 years, had a disease duration of $>$3 years and available data in adulthood. The control group included healthy young people of corresponding age and sex. The patients' medical documentation was retrospectively analyzed, i.e. the age of the disease onset, period from the starting of first clinical signs up to the moment of making diagnosis, activeness of the disease in its debut and received treatment in childhood. Upon reaching adulthood, all patients were examined either as inpatients or outpatients in Oleksandrivska City Clinical Hospital, Kyiv, Ukraine during the period from April 2015 to December 2016. The duration of the disease, education, employment record, the ILAR subtypes, as well as the presence of rheumatoid factor (RF), anti-citrullinated protein anti-bodies (ACPA), antinuclear factor (ANF), human leukocyte antigen (HLA) B27, activeness of the disease in childhood according to the Juvenile Arthritis Disease Activity Score (JADAS), number of swollen joints, duration of morning stiffness, systemic manifestations, presence of uveitis, rash, fever, the erythrocyte sedimentation rate (ESR) (mm/h), C-reactive protein (CRP) (mg/l) were estimated. The evaluation of patient and physician's global assessment of disease activity (VAS 0-10cm), the Short Form Health Survey-36 (SF-36) and the Health Assessment questionnaire (HAQ), current and previous therapy with corticosteroids, disease-modifying antirheumatic drugs (DMARDs) and immunobiological therapy (IBT) were considered as well. The diagnosis of each patient was revised according to the adult terminology of rheumatic diseases: rheumatoid arthritis (RA) (according to the 2010 ACR-EULAR classification criteria) [5], ankylosing spondylitis (AS) (1984 Modified New York Criteria for AS) [6], psoriatic arthritis (the CASPAR criteria) [7], Still's disease [8], undifferentiated arthritis, remission [12].

We assessed the activeness of the disease in all patients. Since the JADAS clinical assessment of JIA activeness has certain limitations of appliance [9], especially in patients with affected spine, in addition to the JADAS, there were used specific indices of activeness applied for various diseases in adult rheumatology, i.e. the DAS28 – for patients with RA [10], the ASDAS - for ankylosing spondylitis, the DAS44 - for psoriatic arthritis. The disease was considered as non-active at the DAS28$<$2.6, the DAS44$<$1.6, the ASDAS$<$1.3 [11, 12, 14-16]. In patients with undifferentiated arthritis, the disease was considered as non-active in the absence of active arthritis, fever, rash, serositis, uveitis in normal values of ESR and CRP. The functional condition of patient was measured according to the HAQ scale, where minimal disorder was diagnosed at 0 up to 0.5, moderate disorder was diagnosed at 0.5 up to 1.5, and severe disorder was diagnosed at $>$1.5.

X-ray examination does not fully show the state of the musculoskeletal system in JIA, as soft tissues may be often affected as well [18]. Since extra-articular damage does not have any valid radiological assessment method in adults with JIA, we used the integral Juvenile Arthritis Damage Index (JADI) as a method to measure remote articular (JADI-A) and extra-articular damage (JADI-E) [19]. The JADI-A included micrognathia and a severely limited mobility in the cervical spine and/or peripheral joints, while the JADI-E included cataracts, muscle atrophy, osteoporosis, aseptic necrosis, stria, stunting, diabetes mellites development, amyloidosis, etc.

Continuous covariates were expressed in terms of their mean and standard deviation (SD). Categorical covariates were described by frequency distribution, and validity of differences by means of the t-test. A p value was considered significant at $p<0.05$. All analyses were performed using Statistica 6.0.

2. Results

122 patients, whose demographic and main clinical features are shown in Table 1, were included into the study. The mean age at the last registered visit was 23.5$\pm$8.5 years, and the average disease duration was 12.7$\pm$8.5 years. The mean delay in diagnosis was 16.8$\pm$26.8 months. Most of the patients (69.3%) had disease duration longer than 10 years, and in 22.1% of patients, it exceeded 20 years. Most studied patients (53.3%) were women. Having classified the patients according to the ILAR subtypes, it was concluded that most patients had persistent oligoarthritis (25.4%), RF-negative polyarthritis (20.5%) and enthesitis-related arthritis (16.5%). It is noteworthy saying that psoriatic arthritis was diagnosed in no examined patients and undifferentiated arthritis was found in 4.9% of patients only. The prevalence of antinuclear

antibodies (ANA), RF, ACPA and HLA B27 are shown in Table 1. The mean age at the onset of the disease was 9.3±4.8 years. Most patients had partially completed higher education (47.5%) or obtained complete higher education (31.9%). At the moment of the examination, 65 patients were students, 40 patients were employed, and 17 patients were not permanently employed. 42.6% of patients had JIA related disability. The assessment of the activeness and functional condition showed that at the moment of the examination the majority of patients (60.7%) had active disease, although functional activeness according to the HAQ was mild (0.41±0.5). One third of patients (30.3%) needed a joint prosthesis which is reflected in the integral indices of remote JIA consequences – JADI-A (1.9±4.4), although JADI-E was also high – 0.68±1.4, which was associated with the side effect of glucocorticoids (GCs).

The analysis of the previous treatment showed that almost a half of the patients (43.4%) had taken GCs previously or were taking them at the moment of the examination, 80.3% of patients received a therapy with one or several DMARDs, 12.3% of patients received IBT. Cumulative dose of GCs was 7.3±31.8g, cumulative dose of synthetic DMARDs was 5.45±5.5 and cumulative dose of IBT was 4.1±3.6.

An adult rheumatologist examined all patients with the history of JIA and the diagnosis was revised according to the adult classification of rheumatic diseases. Table 2 shows the transformation of different JIA subtypes into adult rheumatic diseases.

The results of diagnosis revision in 122 adult patients showed that typical diagnostic criteria for RA were estimated in 32.8%, AS – in 31.1% of patients, undifferentiated arthritis – in 13.9% of patients, Still's disease – in 4.9% of patients, psoriatic arthritis – in 0.8% of patients, steady clinical laboratory remission – in 16.5% of patients. Most patients with RF+ polyarticular JIA (81.8%) fulfilled RA criteria in adulthood, and in 85% of patients with enthesitis-related arthritis as well as 53.8% of patients with extended oligoarthritis ankylosing spondylitis developed in adulthood.

We assessed the activeness of the disease in adulthood; determined the HAQ score, the JADI index, and disability status depending on the ILAR classification system for juvenile idiopathic arthritis, which is reflected in Table 3.

According to Table 3, 68.8% of patients with systemic JIA, RF-, 68% of patients with RF- polyarthritic subtype and 55% of patients with enthesitis-related arthritis had disability and incapacitation. Minimal disorders of the patients' general condition according to the HAQ in adult age were found in most ILAR subtypes of JIA (extended and persistent oligoarthritis, RF+ polyarthritis, systemic subtype), and moderate disorders of the general condition were found in enthesitis-related arthritis and RF- polyarthritis. Side effects of JIA according to the JADI-A included severe articular damage being most frequently found in systemic and RF+ polyarthritis subtypes of JIA, while side effects of JIA according to the JADI-E included extra-articular damage being found in systemic and RF- polyarthritis subtypes of JIA, that was confirmed by the assessment of physical health according to the SF-36, which was the worst in patients with systemic (40.3±12.6) and RF- polyarthritis (38.9±9.4) subtypes of JIA.

3. Discussion

There is a limited number of long-term observations of patients with JIA [18, 19], mostly dating back to the pre-biological era. Our research presented observations of Ukrainian adult patients with JIA (the mean duration of the disease was 12.8±8.5 years) including 22.1% of patients with disease duration ≥20 years. We investigated that most patients continued to take DMARDs or undergo IBT, 60.7% of patients had active disease, 22.9% of the studied patients received IBT in childhood or adulthood. This exceeded the data of Selvaag AM, et al, who informed that 41% of patients with JIA had active disease at the age of 30 years, and another investigation registered 37-43% of patients with active disease [18, 19]. Our data coincided with the data presented by Oliveira-Ramos F, et al [3] who registered 67% of patients with active disease in adulthood. The researchers attribute the higher percentage to the fact that to assess disease activeness they applied scales introduced for rheumatic diseases in adulthood. However, they did not observe patients with persistent oligoarthritis, which is different from our investigation. Besides, we included 16.4% of patients in remission. The study presented the correspondence of JIA to the classification criteria for adult rheumatic diseases in adult patients. Only 13.9% of patients were not classified according to adult disease. 81.8% of patients with RF+ polyarthritis in childhood could be classified as RA and 85% of patients with EA as SpA. 25% of patients with systemic subtype of JIA were classified as Still's syndrome in adulthood and 31.3% of patients as RA. Half of patients (50%) with juvenile undifferentiated arthritis reached remission in adulthood, 33.3% of patients developed rheumatoid arthritis, and 16.7% of patients developed spondyloarthritis. Our investigation, however, did not include patients with juvenile psoriatic arthritis, which indicates diagnostic inadequacy of this subtype in childhood. The majority of patients with RF- polyarthritis (68%), systemic arthritis (68%), and enthesitis-related arthritis (55%) had JIA related disability, which indicated an unfavorable clinical course and inadequate therapy for these JIA subtypes. The integral JADI of remote articular and extra-articular damage showed severe articular damage in patients with systemic JIA and RF+ polyarthritis and extra-articular damage in patients with systemic and RF- polyarthritis. This reflected more aggressive course of the disease in these subtypes and the use of higher dose of GCs.

4. Conclusions

The results of our investigation showed that further research of remote consequences of JIA in adult age and long-term observation of such patients require a detailed study to improve diagnostics and provide adequate treatment of rheumatic diseases with juvenile onset in adult age.

Table 1. Clinical description of patients with juvenile idiopathic arthritis

Indices	Patients, n=122 No. (%)/ mean±SD	Control group, n=76
Female	65 (53.3%)	42 (55.2%)
Male	57 (46.7%)	34 (44.7%)
ILAR variant		
Persistent oligoarthritis	31 (25.4%)	
Extended oligoarthritis	13 (10.7%)	
RF-positive oligoarthritis	11 (9.0%)	
RF-negative oligoarthritis	25 (20.5%)	
Systemic JIA	16 (13.1%)	
Enthesitis-related JIA	20 (16.4%)	
Psoriatic arthritis	0	
Undifferentiated arthritis	6 (4.9%)	
Age at the disease onset, years	9.3±4.8	
Time of the delay in diagnosis, months	16.8±26.8	
Age at last consultation, years	23.5±7.1	20.2±2.5
Duration of the disease, years	12.8±8.5	
ANF+ (n=42)	14 (11.5%)	
RF+ (n=122)	30 (24.6%)	
ACPA + (n=60)	6 (10%)	
HLA B27 + (n=122)	33 (27.0%)	
Education		
Secondary	27 (22.1%)	
Partially completed higher	58 (47.5%)	76 (100%)
Higher	39 (31.9%)	
Current professional status		
Studying	65 (53.3%)	76 (100%)
Employed	40 (32.8%)	
Unemployed	17 (13.9%)	
Disability due to JIA	58 (42.6%)	
Activeness of the disease		
Active disease	74 (60.7%)	
Inactive disease	48 (39.3%)	
Need joint prosthesis	37 (30.3%)	
HAQ score	0.41±0.5	0.01±0.1
JADI-A score	1.9±4.4	
JADI-E score	0.68±1.4	
SF-36 PCS	43.2±12.6	56.4±5.5
Previous treatment		
Patients being previously treated with GCs	53 (43.4%)	
Patients being previously treated with synthetic DMARDs	98 (80.3%)	
Patients who previously underwent IBT	28 (23.0%)	
Current treatment		
Patients being previously treated with GCs	36 (29.5%)	
Patients being previously treated with synthetic DMARDs	88 (72.1%)	
Patients undergoing IBT	15 (12.3%)	
Cumulative GCs dose (g) n=77	7.3±31.8	
Cumulative dose of synthetic DMARDs, years, n=115	5.45±5.5	
Cumulative dose of IBT, years, n= 2	4.1±3.6	

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Table 2. Classification according to the adult interpretation of rheumatic diseases

Classification of ILAR subgroup	Adult rheumatic disease registered during the last visit					
	RA	AS	PsA	Still's disease in adults	Non-classified	Remission
Systemic JIA, n=16	5 (31.3%)	4 (25%)	0	4 (25%)	1 (6.3%)	2 (12.5%)
RF-polyarthritis, n=25	13 (52%)	4 (16%)	0	1 (4%)	4 (16%)	3 (12%)
RF+polyarthritis, n=11	9 (81.8%)	0	1 (9.1%)	0	1 (9.1%)	0
Persistent oligoarthritis, n= 31	8 (25.8%)	5 (16.1%)	0	1 (3.2%)	10 (32.2%)	7 (22.6%)
Extended oligoarthritis, n=13	3 (23.1%)	7 (53.8%)	0	0	1 (7.7%)	2 (15.4%)
Enthesitis-related arthritis, n=20	0	17 (85%)	0	0	0	3 (15%)
Psoriatic arthritis, n=0	0	0	0	0	0	0
Undifferentiated arthritis, n=6	2 (33.3%)	1 (16.7%)	0	0	0	3 (50%)
Total number, n=122	40 (32.8%)	38 (31.1%)	1 (0.8%)	6 (4.9%)	17 (13.9%)	20 (16.4%)

Table 3. Disease activeness, the Health Assessment Questionnaire score, the Juvenile Arthritis Damage Index and disability status depending on the International League of Associations for Rheumatology classification system for juvenile idiopathic arthritis

ILAR subtypes	Activeness of the disease - active/non-active	SF-36-score (PCS)*	HAQ score*	JADI-A score*	JADI-E score*	Patients with JIA related disability (%)
Extended oligoarthritis, n=13	7/6	42.7±5.6	0.33±0.22	0.88±1.9	0.16±0.6	4 (30.8%)
Persistent oligoarthritis, n=31	16/15	44.8±8.9	0.26±0.28	0.91±1.9	0.5±1.2	12 (38.7%)
RF+polyarthritis, n=11	10/1	40.6±11.3	0.38±0.53	4.0±5.1	0.44±0.65	2 (18.2%)
RF-polyarthritis, n=25	11/14	38.9±9.4	0.52±0.73	2.8±4.2	1.39±2.14	17 (68.0%)
Systemic JIA, n=16	6/10	40.3±12.6	0.28±0.46	4.9±10.3	1.55±1.9	11 (68.8%)
Enthesitis-related arthritis, n=20	11/9	45.6±18.0	0.61±0.7	0.4±0.9	0.35±0.67	11 (55.0%)
Psoriatic arthritis, n=0	-	-	-	-	-	
Undifferentiated arthritis, n=6	3/3		0.33±0.2			0 (0%)

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