Long-Term Effects of Articular and Extra-Articular Damage in Adult Patients with Juvenile Idiopathic Arthritis and Different Immunogenic Markers

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Abstract
To assess the long-term effects of juvenile idiopathic arthritis in adulthood, unified diagnostic methods for articular and extra-articular lesions should be used which depend on the juvenile idiopathic arthritis variants, the disease activity and treatment.

The objective of the research was to compare the clinical manifestations in adult patients with different juvenile idiopathic arthritis-specific immunogenic markers and to evaluate their impact on the long-term articular and extra-articular damage.

Materials and methods. We observed 132 young patients with different juvenile idiopathic arthritis variants. According to genetic/immunological markers the following groups were formed: Group I - 38 positive human leukocyte antigen B27 patients; Group II - 13 positive antinuclear antibody patients; Group III - 26 positive rheumatoid factor/anti-cyclic citrullinated peptide patients and Group IV - 55 patients with all negative markers. Long-term effects of juvenile idiopathic arthritis were estimated by the articular juvenile arthritis damage index (JADI-A) and the extra-articular juvenile arthritis damage index (JADI-E). Descriptive statistics, the Student's T-test, the Fisher's exact test and Mann-Whitney U-test were performed.

Results. 70 women and 62 men with the disease duration of 13.6±9.3 years at the age of 24.3±8.3 years were included into the study: 12 (9.1%) patients with positive rheumatoid factor polyarthritis, 30 (22.7%) patients - with negative rheumatoid factor polyarthritis, 32 (24.2%) patients with persistent oligoarthritis, 19 (14.4%) patients with enthesitis-related arthritis and 19 (14.4%) patients with systemic arthritis; there were no patients with psoriatic arthritis. There were no differences between groups in age, disease-modifying antirheumatic drug cumulative dose, mean dose of prednisolone and quality of life according to the SF-36. In Group I, the delay in the diagnosis was more than one year (18.6±24.2 months). In this group, less painful (p<0.005) and deformed (p<0.01) joints as compared to Group III, and higher levels of the ESR and C-reactive protein as compared to Group IV were found, although the Juvenile Arthritis Disease Activity Score index in childhood was lower (p<0.005) as compared to Group II. They received a lower cumulative dose of the glucocorticoids as compared to Group II (p<0.01), respectively. They had lower (p<0.01) JADI-E as compared to Group II (1.31±1.49) and lower (p<0.01) JADI-A as compared to Group III. In Group III, the diagnosis was made the fastest in comparison with other groups (6.4±8.4 months, p<0.05); more painful joints (p<0.05) and ankylosis (p<0.05) were observed as compared to Group I, and JADI-A was significantly higher (p<0.05) in Group III as compared to Group I. The most pronounced JADI-A was found in Group III, while in Group I and Group II, this index was the lowest. JADI-E was the most pronounced in Group II, and the most favorable course was found in Group I and Group III (p<0.05).

Conclusions. Presence of anti-cyclic citrullinated peptide/rheumatoid factor in adults with juvenile idiopathic arthritis has negative impact on joint damage (JADI-A) indicating the need for aggressive therapy in both childhood and adulthood. Presences of antinuclear antibodies are associated with more often extra-articular damages in adulthood as compared to other groups.

Keywords
RF; HLA-B27; A-CC; ANA; adult juvenile idiopathic arthritis; long-term effects

Problem statement and analysis of the recent research
The clinical course of juvenile idiopathic arthritis (JIA) depends on one of the seven JIA variants. However, JIA is usually unpredictable and can lead to the disease remission as well as to severe complications and hence handicaps and social incapacitation in both childhood and adulthood. To evaluate long-term effects of JIA in adulthood, we should use unified methods to diagnose articular and extra-articular damage. They depend not only on JIA variant, disease activity, and the level of damage to the target organ due to the pathologic process, but also on the received therapy, its ef-
We observed 132 young patients with different JIA variants and the Disease Activity Score-28 (DAS 28), the Juvenile Arthritis Disease Activity Score Index (JADI) for articular (JADI-A) and extra-articular (JADI-E) JIA. They included the assessment of functional disorders or the development of ankyloses, the presence of protheses in the temporomandibular joints, the cervical spine, the shoulder joints, the elbow joints, the radiocarpal joints, the metacarpophalangeal joints, the proximal interphalangeal joints, the hip joints, the knee joints, the talocrural joints, and the metatarsal phalangeal joints. The evaluation of long-term extra-articular effects of JIA focused on eye lesions (the presence of cataract and/or other uveitis complications with vision loss), the musculoskeletal system (the development of considerable muscle atrophy, osteoporosis with vertebral fractures or compressions, asptic necrosis of bones, severe spinal curvature deformation due to the contraction of the hip joint or change in extremity length, significant change in extremity length or bone growth problems), the skin (stria, atrophy of hypodermic tissue due to the intra-articular injection of corticosteroids), the endocrine system (growth disorders, pubertal development disorders, diabetes mellitus) and the development of amyloidosis. In addition to the clinical picture, there are certain immunological markers used for the diagnostics of different JIA variants, i.e., positive or negative rheumatoid factor (RF), immunoglobulin G (IgG) antibodies to cyclic cytrullinated peptide (A-CCP), antinuclear antibody (ANA), human leukocyte antigen B27 (HLA-B27). The research of their impact on the long-term effects of JIA in adulthood is of great importance.

The objective of the research was to compare clinical symptoms and received therapy in adult patients with different JIA specific immunogenic markers (RF, A-CCP, ANA, NLA-B27), as well as to evaluate their influence on the development of long-term articular and extra-articular damage.

### 1. Materials and methods

We observed 132 young patients with different JIA variants in the Oleksandrivska Municipal Clinical Hospital, Kyiv. The patients’ height, weight, body mass index (BMI), the delay in the diagnosis from the onset of clinical manifestations, disease duration, disease activity in childhood and adulthood according to the Juvenile Arthritis Disease Activity Score (JADAS) [1] and the Disease Activity Score-28 (DAS 28), the patients’ general condition in childhood and adulthood according to the visual analogue scale (VAS), treatment with GC and disease-modifying antirheumatic drugs (DMARDs), as well as immune-biological therapy (IBT) received in childhood were analyzed. We studied medical documentation to determine the localization of joint syndrome in childhood and adulthood, the presence of enthesisitis, sacroilitis, spinal pain, uveitis in both childhood and adulthood. Quality of life was evaluated using the 36-Item Short Form Health Survey (SF-36) and the degree of functional impairment was assessed using the Health Assessment Questionnaire (HAQ). Long-term effects of JIA were estimated by the articular juvenile arthritis damage index (JADI-A) and the extra-articular juvenile arthritis damage index (JADI-E) [12].

All patients underwent fasting blood tests for the following indices: quantitative C-reactive protein (CRP) (latex test, Roche Diagnostics), HLA-B27 (flow cytometry method on the FACScan using monoclonal anti-HLA B27 antibodies (Becton Dickinson), RF (Immunoglobulin M (IgM) autoantibodies to Fc fragment of IgG) using the Euroimmun enzyme-linked immunosorbent assay (ELISA), IgG antibodies to A-CCP by flow cytofluorometry using BioPlex 2200 testing (the Bio-Rad testing system), and ANA by immunofluorescence method using the Euroimmun EUROStar III Plus.

Statistical analysis was performed using descriptive statistics, the Student’s t test for random sampling, the Fisher’s exact test for small sample size. The comparison of parametric indicators was performed using the Mann-Whitney U test, since the distribution of the samples’ parametric indices was not Gaussian (according to the Shapiro-Wilk test). We used the program "Statistica 6.0" Copyright© StatSoft, Inc. 1984-2001.

### 2. Results

There were 70 women and 62 men at the age of 24.3±8.3 years with the disease duration of 13.6±9.3 years. The average height was 1.70±1.08 m, body weight - 62.3±14.9 kg, the BMI - 21.±13.5. According to International League of Associations for Rheumatology (ILAR) classification of JIA, there were 12 (9.1%) patients with RF (+) polyarthritis, 30 (22.7%) patients with RF (-) polyarthritis, 32 (24.2%) patients with persistent oligoarthritis, 19 (14.4%) patients with extended oligoarthritis, 20 (15.2%) patients with enthesitis-related arthritis, and 19 (14.4%) patients with systemic arthritis; there were no patients with psoriatic arthritis. The analysis of immunological marker frequency in different JIA variants showed the following results: HLA-B27 was detected in 38 (28.8% of all patients with JIA) patients, RF and/or A-CCP - in 26 (19.6%) patients, ANA - in 13 (9.8%) patients; all the markers were negative in 55 (41.7%) patients.

To detect the difference between patients with different immunologic/genetic markers irrespective of the ILAR variant of JIA, we formed groups of adult patients with JIA according to specific genetic/immunologic markers, i.e., Group I - 38 HLA-B27 positive patients; Group II - 13 ANA positive patients; Group III - 26 RF and/or A-CCP positive patients; and Group IV - 55 patients with all negative markers (Table 1).

Table 1 demonstrates that there was no difference between groups in age, DMARD cumulative dose, mean dose
of prednisolone and quality of life according to the SF-36 questionnaire. However, in HLA-B27 positive patients, the disease started at an older age (12.3±3.3 years of age) than in other groups (p<0.005) and its duration was lower (9.5±6.9 years) in comparison with other groups (p>0.05), although the delay in the diagnosis from the onset of clinical manifestations was noted more often (p<0.005) than in the group of RF/A-CCP positive patients.

In HLA-B27 positive patients, the delay in the diagnosis was more than one year (18.6±24.2 months). In this group, less painful (p<0.005) and deformed (p<0.005) joints were found as compared to RF and/or A-CCP positive patients, and higher levels of the ESR (21.6±17.5 mm/h) and CRP (28.4±42.9 mg/h) were registered as compared to Group IV (11.3±11.9 mm/h and 7.3±10.9 mg/h, respectively), although the JADAS index in childhood was lower (p<0.005) as compared to ANA positive patients. Thus, due to the lower laboratory and clinical data they received a lower (p<0.005) cumulative dose of GC (2203.9±4546.9 mg) as compared with ANA positive patients (6516.6±5396.2 mg). That is probably the reason of lower (p<0.005) long-term extra-articular damage index in adulthood (JADI-E) (0.50±1.06 mg) as compared to ANA positive patients (1.31±1.49) and lower (p<0.005) long-term articular damage index (JADI-A) in adulthood as compared to A-CCP/RF positive patients (3.0±4.9).

In the group of A-CCP/RF+ patients, the diagnosis was made the fastest in comparison with other groups (6.4±8.4 months, p<0.05), they had more painful joints (p<0.05) and ankyloses (p<0.05) as compared to HLA-B27+ group. This contributed to a significantly higher JADI-A (p<0.05) in A-CCP/RF+ patients as compared to HLA-B27+ group.

The most pronounced joint damage (JADI-A) in adults with JIA was found in the group of A-CCP/RF positive patients, whereas in HLA-B27 and ANA positive patients, this index was the lowest with less long-term effects. Extra-articular damage (JADI-E) was the most pronounced in the group of ANA-positive patients, and the most favourable course was found in A-CCP/RF and HLA-B27 positive patients (Fig. 1).

### 3. Discussion

132 adult patients with JIA were included in the study (with the mean disease duration of 13.6 ± 9.3 years). 21.2% of patients had disease duration ≥20 years. There are scarce long-term observations of patients with JIA [6, 8, 9, 13] mostly carried out in pre-biologic era. 21.9% of patients included in our study underwent IBT in childhood or adulthood and most patients continued to take DMARDs or undergo IBT. 59.9% of adult patients had active disease. This exceeded the data presented by Selvaag AM, et al [9], who informed that 41% of patients with JIA had active disease after 30 years of observation, as well as the data of another investigation, which registered 37-43% of patients with active disease [13]. Oliver’s-Ramas et al. [5] registered 67% of patients with active disease in adulthood. The researchers attribute the higher percentage to the fact that to assess disease activity, they applied scales introduced for rheumatic diseases in adulthood. However, unlike our research, they did not observe patients with more favourable JIA prognosis - persistent oligoarthritis most of whom develop remission. Our study is consistent with the research carried out by other scientists who investigated prognostic unfavourable factors for the clinical course of rheumatoid arthritis. These are positive RF and/or A-CCP alongside with a high disease activity and early structural damage [2, 11]. Although these data refer to the prognosis of rheumatoid arthritis, our research confirmed the hypothesis of negative influence of RF and/or A-CCP based on the study of JIA patients [3].

### 4. Conclusions

Despite the early diagnosis in childhood, in adults with RF/A-CCP (+) JIA, greater number of joints were damaged and deformed as compared to other groups.

The most pronounced joint damage (JADI-A) as a result of JIA in adulthood was found in A-CCP/RF (+) patients indicating the need for aggressive therapy in both childhood and adulthood.

ANA (+) patients with JIA more often develop extra-articular damage in adulthood, which is probably due to the higher disease activity according to the JADAS in childhood and higher cumulative dose of glucocorticoids as compared to other groups.

### 5. Prospects for further research

Further researches of prognostic unfavourable factors in adult patients with JIA are needed.

### Conflict of Interest

None declared. The authors claim no conflict of interest likely to cause damage to the unbiased approach of the research.
Table 1. Distribution of adult patients with JIA according to specific genetic/immunologic markers

| Indices                                      | HLA-B27 M±SD, n=38 (Group I) | ANA M±SD, n=13 (Group II) | A-CCP /RF M±SD, n=26 (Group III) | All markers negative M±SD, n=55 (Group IV) |
|----------------------------------------------|------------------------------|---------------------------|-------------------------------|-------------------------------------------|
| Age at the moment of examination, years      | 23.6±6.7                     | 20.8±3.9                  | 23.7±7.3                     | 22.9±7.2                                  |
| Height, m                                    | 1.7±0.1                      | 1.7±0.1                   | 1.7±0.1                      | 1.7±0.1                                   |
| Weight, kg                                   | 68.9±13.0*                   | 57.2±9.7                  | 59.2±9.9***                  | 60.7±16.2**                               |
| BMI, kg/m2                                    | 22.3±4.33                    | 20.4±2.35                 | 20.48±2.38                   | 21.13±3.80                               |
| Age in the debut of the disease, years       | 12.3±3.3*                    | 9.9±4.9                   | 9.5±3.8**                    | 7.5±5.1***                                |
| Period of delay in the diagnosis, months     | 18.6±24.2                    | 28.9±46.9#                | 6.4±8.4**                   | 14.1±23.9                                 |
| Duration of the disease, years               | 9.5±6.9                      | 10.9±7.4                  | 13.9±7.7***                  | 14.6±9.1***                               |
| Painful joints (number)                      | 3.3±3.6                      | 2.7±4.5                   | 6.2±5.9**                    | 2.1±3.7                                   |
| Deformed joints/ ankyloses (number)          | 0.4±1.0                      | 0.8±1.5                   | 1.7±2.9**                    | 0.9±1.8                                   |
| ESR in the debut of the disease, mm/h        | 45.3±91.0                    | 21.3±15.4                 | 26.3±17.8                    | 29.2±22.3                                 |
| ESR at the moment of examination, mm/h       | 21.6±17.5                    | 17.0±17.2                 | 22.8±20.3                    | 11.3±11.9***                              |
| CRP in the debut of the disease, mg/l        | 25.6±26.5                    | 19.6±19.7                 | 24.4±33.3                    | 31.1±29.2                                 |
| CRP at the moment of examination, mg/l       | 28.4±42.9                    | 22.1±51.2                 | 24.9±41.2                    | 7.3±10.9***                               |
| Patient’s/doctor’s evaluation of general condition in childhood (VAS), mm | 62.5±21.7/ 52.1±18.2 | 77.1±16.0/ 61.4±10.7 | 60.0±23.3/ 52.5±19.1 | 68.4±21.6/ 54.4±19.0 |
| Patient’s/doctor’s evaluation of general condition in adulthood (VAS), mm | 40.5±25.3/ 33.4±24.6 | 38.9±21.8/ 31.5±24.1 | 36.9±17.9/ 32.5±25.6 | 33.1±25.1/ 24.8±21.6 |
| DAS28 in adulthood                           | 3.2±1.5                      | 2.9±1.3                   | 3.7±1.5&                     | 2.7±1.3                                   |
| JADAS in childhood                           | 12.9±6.6*                    | 19.3±6.0                  | 15.0±7.5                     | 15.3±9.1                                  |
| JADAS in adulthood                           | 9.1±6.2                      | 10.8±6.9&                 | 10.7±9.1&                    | 7.1±5.3                                   |
| Permanent dose of prednisolone, mg           | 5.8±2.4                      | 9.0±12.5                  | 9.2±5.8                      | 3.7±5.7                                   |
| Cumulative dose of GC, mg                   | 2203.9±4546.9*               | 6516.6±5396.2             | 4475.7±7598.4                | 12443.3±48063.6                           |
| Cumulative dose of DMARDs, years             | 4.9±4.9                      | 5.1±3.4                   | 5.4±6.4                      | 5.5±5.8                                   |
| JADI-A                                       | 1.1±1.9                      | 0.9±2.3                   | 3.0±4.9**                    | 1.9±5.1                                   |
| JADI-E                                       | 0.50±1.06*                   | 1.31±1.49#                | 0.38±0.7                     | 0.73±1.55                                 |
| Quality of life according to SF-36 PCS/MCS   | 44.0±11.3/ 45.6±13.5         | 47.3±9.6/ 46.1±10.6       | 44.3±7.9/ 46.0±9.5           | 45.6±10.3/ 46.5±9.6                       |

Notes:

ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; VAS – visual analogue scale; BMI – body mass index; GC – glucocorticoids; JADI-A – articular juvenile arthritis damage index; JADI-E – extra-articular juvenile arthritis damage index; JADAS – Juvenile Arthritis Disease Activity Score;

* – reliable differences (p<0.05) between HLA-B27- and ANF-positive patients;
** – reliable differences (p<0.05) between HLA-B27- and A-CCP/RF-positive patients;
*** – reliable differences (p<0.05) between HLA-B27-positive and all other markers negative patients;
# – reliable differences (p<0.05) between ANA- and A-CCP-positive patients;
& – reliable differences (p<0.05) between A-CCP/RF-positive and all markers negative patients.

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