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Keywords: Juvenile Idiopathic Arthritis, onset mode, early diagnosis, stage-related treatment

INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) is the most frequent pediatric rheumatic disease, with an incidence varying from 0.8 to 22 in 100.000 children. JIA can determine important chronic morbidities that include ponderal hypotrophy, delayed puberty, affectation of articular mobility and ankylosis.

The evolution of the JIA forms in unpredictable; most of the times it is undulatory, the periods of disease activity are separated by periods of remission. Arthritis persists in adult life, continuing to cause pain, functional impotence and disability.

Normal development of children with JIA represents the fundamental objective of doctors. This presupposes an efficient control of the disease through an early diagnosis, from the first stages of the disease, and a prompt and adequate treatment of the disease subtype.

Results of studies in the last years suggest that early and aggressive treatment with *DMARD (Disease-modifying antirheumatic drugs)* ca delay or stop the onset of erosions and can increase the probability of remission. The optimal drug therapy involves the recognition of the disease subtypes that have different etiology, pathology, prognosis and response to treatment [2].

On the other hand, the clinical evaluation of Juvenile Idiopathic Arthritis is polymorphous; it mimics the early stages of diseases that are more or less severe, thus there is the risk that a definitive diagnosis be established only later, sometimes years after the onset of the disease.

Therefore, a better evaluation starting with the first signs of disease, that can be done when the patient is first admitted, will lead to a correct and full diagnosis, allowing thus for the administration of the treatment best suited for the specific type of JIA.

We consider that the onset and evolution mode of JIA is of particular interest not only for the pediatric or rheumatologist physician/practitioner, but also for the research domain for this disease, and it represents a motivation for the desire to study such aspects of the disease.

This study offers information with practical applicability, with a goal to establish the therapeutic conduct in relation to the profile of the child with JIA (profile based on the onset mode, genetic predisposition, clinical and paraclinical features) and to the subsequent evolution of the case. The purpose is to increase the quality of the evaluation system for persons with JIA and, thus, the quality of the therapeutic conduct; the central theme is the evaluation of the impact of the onset mode on the subsequent evolution of JIA.

THEORETICAL PART

It is dedicated to the analysis of current literature knowledge that regards the definition and classification of JIA, the epidemiology and etiopathology, the clinical manifestations and paraclinical examinations, the positive and definite diagnosis, as well as the evolution and complications of the disease. A special chapter is dedicated to the therapy of juvenile arthritis, starting with non steroidal and steroidal anti-inflammatory drugs, remissive and biological medication, diet and physiotherapy, occupational therapy and psychotherapy, as well as the stage-related treatment of different JIA subgroups.

PURPOSE AND OBJECTIVES OF THE THESIS

The purpose of the thesis is to render efficient the diagnosis of Juvenile Idiopathic Arthritis (JIA), by studying the clinical, immunological and radiological particularities, as well as the evolution of the disease, in relation to the core treatment administered.

Objectives:

1. Analysis of the epidemiological factors (demographic data, personal physiological history, other trigger factors) in patients with JIA.
2. Clinical, biological and evolutionary analysis of patients with JIA.

3. The impact of the JIA onset mode on the evolution of patients.
4. Analysis of the therapy administered to patients with JIA.

MATERIAL AND METHOD – general considerations

The group that was studied comprised 173 patients, admitted in the Pediatric Departments from Craiova, Tirgu-Jiu and Rimnicu Vilcea in the period between 2000 and 2009, as well as in the Institutul de Ocrotire a Mamei și Copilului „Alfred Rusescu" from Bucharest, in the period between 2000 and 2006. The study was clinically and statistically retrospective in the period between 2000 and 2004, consisting in selection of data from consultation sheets and follow-up records, and prospective in the period between 2005 and 2010.

Sub-study I

The group included 173 patients registered with the Pediatric Departments from Craiova, Tirgu-Jiu and Rimnicu Vilcea and with the Institutul de Ocrotire a Mamei și Copilului „Alfred Rusescu" from Bucharest. Sub-study I was mixed: retrospective for the period 01/01/2000-12/31/2004, consisting in selection of data from consultation sheets and follow-up records, and prospective for the period 2005- 2010.

The JIA patients were selected according to the ILAR criteria: a) systemic arthritis; b) persistent oligoarthritis; c) extensive oligoarthritis; d) seropositive polyarticular JIA; e) seronegative polyarticular JIA; f) arthritis associated to enthesitis; g) psoriatic arthritis; h) undifferentiated arthritis.

The group was divided, in relation to the form of JIA, into:

- Patients with an undifferentiated type of arthritis
- Patients with the systemic type
- Patients with the extensive oligoarticular type
- Patients with the persistent oligoarticular type
- Patients with the seropositive polyarticular type
- Patients with the seronegative polyarticular type
- Patients with spondyloarthropathy

The objectives of sub-study I were:

1. Analysis of the epidemiological factors (demographic data, physiological personal history, other trigger factors) in patients with JIA.
2. Clinical, biological and evolutionary analysis of patients with JIA.
3. Analysis of the therapy administered to patients with JIA.

Selection criteria

Criteria for the inclusion into the study:

- consent of the patient to participate;
- age 16 years;
- patients had to be diagnosed with Juvenile Idiopathic Arthritis according to the ILAR (International League Against Rheumatism) criteria established in Durban in 1997 and revised in Edmonton in 2001.

Exclusion criteria:

- *for systemic arthritis*: a) other diseases with systemic manifestations; b) psoriasis or positive family history for first degree relatives; c) arthritis in a boy older than 6 years with positive HLA-B27; d) ankylosing spondylitis, arthritis associated with enthesitis, sacroiliitis associated with inflammatory bowel disease, Reiter's syndrome or positive family history for these diseases; e) positive RF in two consecutive assessments.
- *for pauciarticular arthritis*: a) cases with family history of psoriasis; b) positive family history for HLA-B27; c) cases with positive rheumatoid factor; d) cases with criteria for systemic JIA; e) ankylosing spondylitis, arthritis associated with enthesitis, sacroiliitis associated with inflammatory bowel disease, Reiter's syndrome or positive family history for these diseases.
- *for psoriatic arthritis*: a) the presence of the rheumatoid factor; b) presence of systemic JIA; c) ankylosing spondylitis, arthritis associated with enthesitis, sacroiliitis associated with inflammatory bowel disease, Reiter's syndrome or positive family history for these diseases; d) arthritis in a boy older than 6 years with positive HLA-B27.
- *for RF-positive polyarticular arthritis*: a) psoriasis or positive family history for first degree relatives; b) presence of systemic JIA; c) ankylosing spondylitis, arthritis associated with enthesitis, sacroiliitis associated with inflammatory bowel disease, Reiter's syndrome or positive family history for these diseases; d) arthritis in a boy older than 6 years with positive HLA-B27.

- *for RF-negative polyarticular arthritis*: a) cases with family history of psoriasis; b) positive family history for HLA-B27; c) cases with positive rheumatoid factor; d) cases with criteria for systemic JIA; e) ankylosing spondylitis, arthritis associated with enthesitis, sacroiliitis associated with inflammatory bowel disease, Reiter's syndrome or positive family history for these diseases.

- *for arthritis associated with enthesitis:* a) presence of the rheumatoid factor; b) presence of systemic JIA; c) psoriasis or positive family history for first degree relatives.

Sub-study II

Sub-study II was prospective; it was carried out in the period 01/01/2005- 01/01/2010, on 3 groups of patients from the three most frequent types of JIA:

- Group S – 15 patients with systemic type JIA;

- Group P – 15 patients with polyarticular type JIA;

- Group O – 15 patients with oligoarticular type JIA.

The patients with JIA were selected according to the ACR criteria, for which the clinical, laboratory and radiological factors at the onset of the disease were evaluated.

Sub-study II has monitored the impact of the JIA onset mode on the evolution of the patients.

The reevaluation of the patients was made at the ages of 1, 2 and 3, according to a special protocol that included the evaluation of the general state, the degree of disease activity and the articular affectation in relation to the functional state or radiological modifications.

Monitored parameters

The diagnosis of juvenile arthritis was suggested by the medical history and the clinical examination, and was confirmed by the laboratory examinations; thus, all patients met the ILAR criteria established in Durban in 1997 and revised in Edmonton in 2001.

The purpose of the patients' **medical history** was to establish:

- demographic and anthropometric parameters: age, sex, background;

- significant family history: rheumatoid polyarthritis, acute articular rheumatism, ankylosing spondylitis, psoriasis, sacroiliitis, uveitis etc.;

- personal physiological history: weight at birth, duration of breast feeding;

- personal pathological history: repeated infections in the first years of life, trigger factor;

- symptoms: arthralgias, number of painful joints, number of tumefied joints, number of joints with limited movement, duration of morning rigidity, physical asthenia, muscle weakness, presence of extra-articular manifestations;

- we have also used other data obtained from the medical history: age of the patients at the onset of the disease and for how long the disease has been active, presence of associated diseases and extra-articular manifestations (elements backed by paraclinical examinations), previous medication.

During **the physical examination**, we have highlighted: the general state, the temperature and weight curves, the number of painful joints, the number of tumefied joints, the number of joints with limited movement, the number of joints with ankylosis, the presence of extra-articular manifestations (asthenia, muscle weakness, adenopathies, hepatomegaly / splenomegaly, myalgias, muscle hypotrophy/atrophy, rash, uveitis, subcutaneous nodules, pleuritis, pericarditis, tendon involvement), the evaluation of the functional state, the neurological and psychological state.

The **paraclinical examinations** done on the patients included in the study were:

A. biological and biochemical: complete blood count (hemoglobin = Hb, erythrocyte indices, white blood cells, thrombocytes), acute phase reactants (ESR, CRP, fibrinogen), serum proteins electrophoresis;

B. immunological assessments: rheumatoid factor (RF), antinuclear antibodies (ANA), immunogram, serum complement, HLA typing;

C. other serum and biochemical analyses: transaminases, urea, creatinine, urinalysis, hypocalcaemia, sideremy.

D. imaging: radiological examination of the joints involved, pulmonary radiography, abdominal ultrasound, musculoskeletal ultrasound, cardiac ultrasound, articular scintigraphy, nuclear magnetic resonance, cranial computed tomography.

E. other examinations: ophthalmic examination, articular puncture, EKG, cardiac examination.

The **assessment of disease activity** was done using the DAS28 index.

The **assessment of functional capacities** was done with the CHAQ (Childhood Health Assessment Questionnaire) index and the Steinbrocker classification.

The **assessment of articular and extra-articular damage** was done using the JADI-A and JADI-E indices respectively.

Statistical analysis

The statistical analysis of the data followed the protocol of an observational clinical study and was done with the EpiInfo program (CDC Atlanta).

The analysis was done both on the whole group, and on interest groups, according to the objectives of the study. The comparison of the differences between the two groups was done using the Student's t-test for groups from normal distributions, and the nonparametric Mann-Whitney U test when the assumption of normal distribution was not plausible. As far as the comparison of three or more groups is concerned, the analysis of variance (ANOVA) was used for normally distributed variables, while the nonparametric Kruskal-Wallis test was used for variables without normal distribution. Qualitative variables were described using absolute or percentual frequency. The comparison between groups was made through the $\chi 2$ test or Fisher's exact test.

RESULTS AND DISCUSSIONS

From a total of 173 children with JIA, the systemic type was confirmed in 15% of the patients, the seronegative polyarticular type in 27.2% of the patients, the RF+ polyarticular type in 4.6% of the patients, the extensive oligoarticular type in 5.2% of the patients, the persistent oligoarticular type in 42.8% of the patients, spondyloarthropathies in 3.5% of the cases, and undifferentiated arthritis in 1.7% of the cases.

JIA affects mostly females, but it varies in relation to the type of JIA.

In young ages – under 5 years old – the onset is especially in the systemic form (46%), followed by the extensive oligoarticular form (33.33%), while the other forms have a higher incidence in the 11-14 years old group. The youngest age at onset was registered for the systemic type – 2 years.

The onset of JIA was preponderantly insidious – 114 cases (65.89%), while the sudden onset was characteristic for the systemic arthritis. Articular affectation was the onset mode for most of the patients (84.97%). In the analysis of the articular affectation, the findings showed that all articulations are affected, the frequency of articular affectation depending on the type of arthritis.

Extra-articular manifestations, along with articular affectation, occupy an important role in JIA and they are characteristic for the systemic type.

Anemia, thrombocytosis and acute phase reactants had elevated values in the study, mostly in the systemic type.

The RF was positive in all children in the RF+ polyarticular type and registered low values in the oligoarticular types. ANA were present in less than 40% of the cases, especially in the extensive oligoarticular type (37.5%) and the persistent type (24.59%). Modifications in the indices of the immune system show an increase in the levels of the third component of the complement (C_3) and an increase in the concentration of serum globulins.

The findings of the imaging examinations in sub-study I have revealed modifications of the articular radiography in 44.08% of the radiographies, especially in the RF+ polyarticular type.

The evaluation of the functional capacities made with the Steinbrocker classification has registered in children with JIA a higher frequency of the Steinbrocker functional class II – 107 children (61.8%), followed by the functional class III – 51 children (29.5%). Functional deficit is most frequently found in the systemic type and the RF+ polyarticular type.

In relation to the DAS28 composite index, the structure of the entire group studied was dominated by medium-activity JIA (62.5%) and low-activity JIA (25.4%).

Sub-study II

Disability was present in 53.33% of the cases (Steinbrocker stage II-IV), 20% had stage III-IV disability, 2.22% of the patients were in stage IV. 3 years after the diagnosis, radiological articular modifications were highlighted in 42.22% of the patients.

The highest average of the DAS28 index was registered in the polyarticular type, 1 year after the diagnosis (5.2807). Final DAS28 values are higher for girls, which highlights the fact that the feminine gender is an unfavorable prognosis factor.

3 years after the diagnosis, the CHAQ score is on average 0.423, with no disabilities present in 16 of the patients (35.55%), while a CHAQ score of 0.5-1.5 is present in 8 patients (17.77%). In the study, the CHAQ score is correlated to the ESR values, the radiological modifications and the visual analog scale for parents and for the physician.

3 years after the onset, the articular damage shown by the JADI-A score is present in 15 patients (33.33%), while the extra-articular damage shown by the JADI-E score was present in 24 patients (53.33%).

For the entire group of JIA patients in the study, JADI-A is correlated with the articular score, CHAQ and the visual analog scale for parents and for the physician. The articular score is positively correlated with articular damage, thus a high articular score represents an unfavorable prognosis factor for the subsequent evolution of JIA cases. JADI-E is positively correlated with the Steinbrocker classification, the DAS28 index, ESR and functional disability.

For the entire group of JIA patients in sub-study II, clinical and biological remission was present in 13 patients (28.88%), 3 years after the diagnosis.

CONCLUSIONS

1. From a total of 173 children with JIA, the systemic type was confirmed in 15% of the patients, the seronegative polyarticular type in 27.2% of the patients, the RF+ polyarticular type in 4.6% of the patients, the extensive oligoarticular type in 5.2% of the patients, the persistent oligoarticular type in 42.8% of the patients, spondyloarthropathies in 3.5% of the cases, and undifferentiated arthritis in 1.7% of the cases.

2. The onset for the systemic and extensive oligoarticular types is at young ages – under 5 years old, while the other types present the highest incidence in the 11-14 years old group. The youngest age at onset was registered for the systemic type – 2 years.

3. The onset of JIA was sudden in 59 cases (34.1%), being characteristic for the systemic type, and insidious in 114 cases (65.89%).

4. Articular affectation was the onset mode for 84.97% of the patients. In the analysis of the articular affectation, the findings showed that all articulations are affected, the frequency of articular affectation depending on the type of arthritis.

5. Extra-articular manifestations are associated with the systemic type and more rarely with the polyarticular and oligoarticular types.

6. Acute phase reactants (EST, CRP, fibrinogen, serum globulins) had elevated values in all types of JIA; the highest values were recorded for the systemic type.

7. Radiological modifications were registered in 44.08% of the cases, with an elevated frequency for the RF+ polyarticular type.

8. *The evaluation of the functional capacities* made with the Steinbrocker classification has registered in children with JIA a higher frequency of the Steinbrocker functional class II – 107 children (61.8%), followed by the functional class III – 51 children (29.5%).

9. In sub-study II, disability was present in 53.33% of the cases (Steinbrocker stage II-IV), 20% had stage III-IV disability, 2.22% of the patients were in stage IV.

10. 3 years after the diagnosis, radiological affectation was highlighted in 19 patients (42.22%), the most affected type being the polyarticular one – 10 cases (22.22%).

11. 3 years after the diagnosis, the CHAQ score is on average 0.423, 16 patients (35.55%) present no disabilities and there are no cases of high CHAQ disability >1.5. The CHAQ score is correlated to the ESR values, the radiological modifications and the visual analog scale for parents and for the physician.

12. For the entire group of JIA patients in the study, JADI-A is correlated with the articular score, CHAQ and the visual analog scale for parents and for the physician. JADI-E is positively correlated with the Steinbrocker classification, the DAS28 index, ESR and CHAQ.

13. High articular score, feminine gender, high levels of ESR, young age at onset for the systemic type and age over 12 for the other types represent unfavorable prognosis factors.

14. For the entire group of JIA patients in sub-study II, remission was present in 13 patients (28.88%), 3 years after the diagnosis.

15. We hope that our findings contour the JIA profile for the monitored area, suggesting the therapeutic options that could determine the favorable evolution of this disease. Establishing an early diagnosis and establishing the type of JIA allows individualizing and monitoring patients and administering the treatment best suited for the specific type of JIA.