Later-onset rheumatoid factor negative polyarticular juvenile idiopathic arthritis (JIA): a unique patient group?

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Abstract

Objective

To determine the two-year outcome of patients with later-onset polyarticular rheumatoid factor (RF) negative (-) juvenile idiopathic arthritis (JIA), and predictors of outcome.

Methods

All patients ages 10 to 16 years diagnosed and followed in the Rheumatology Clinic at SickKids Hospital with the diagnosis of polyarticular RF- JIA were eligible for study. A retrospective chart analysis was performed and number of active joints, medications, laboratory information and childhood health assessment questionnaire scores were recorded at diagnosis, and 6, 12, and 24 months following diagnosis.

Results

As early as 6 months after diagnosis the mean number of active joints decreased from 16 to < 10, with 50% of the patients having < 5 active joints. The predominant joints affected were the wrist, knee, and small joints of the hand. The only predictor of active joint count at the 2-year follow-up was initial presenting active joint count as classified as mild, moderate, or severe. Sex, age, and laboratory results at presentation did not show any correlation with active joint count at 2 years. Majority of patients were treated with non-steroidal anti-inflammatory drugs (98%) and at least one disease-modifying anti-rheumatic drug (56%).

Conclusions

The two-year outcome of patients with late-onset RF- polyarticular JIA was very good with the majority of patients having minimally active disease at last follow-up. Presence of significant polyarthritis at presentation was the only feature associated with long-term joint activity. Sex and lab results did not show any correlation with active joint in this cohort of RF- JIA patients.

Key words

juvenile idiopathic arthritis, outcome, epidemiology, physical function.
Introduction
Juvenile idiopathic arthritis (JIA) is the current term used to describe patients with onset of chronic arthritis beginning prior to the age of 16 that persists for 6 weeks or greater without a known cause. The most commonly used classification system is the International League of Associations for Rheumatology (ILAR) classification criteria for JIA that divides JIA into 7 separate categories; each of which attempts to define a unique group of patients who have differentiating signs and symptoms occurring over the first 6 months (1). A reason for separating JIA into these sub-groups is the assumption that each of the 7 sub-types has a different course, outcome and/or pathophysiology. This assumption is borne out in studies showing that patients with oligoarticular course JIA have a better short-term and long-term outcome than patients with polyarticular-course JIA (2-5); the outcome of extended oligoarticular differs from that of persistent oligoarticular JIA (6); patients with systemic JIA (SJIA) uniquely have fevers and rash and have a different response to biologics than patients with other forms of JIA (7); and patients with enthesitis-related arthritis (ERA) have different genetic susceptibility and clinical phenotype than other sub-types of JIA (8, 9). However, there are few large studies examining the other individual groups separately.

Polyarticular JIA is defined as involvement of five or more joints within the first six months of disease and can be divided into RF- and RF+ according to presence or absence of IgM RF (1). In addition patients with either oligoarticular JIA or SJIA may also have a polyarticular course and these patients are usually included in therapeutic drug trials as it is assumed that the course and/or response to therapy is similar in all of these groups of patients. This assumption has yet to be proved. To further complicate the issue, patients with RF- polyarticular JIA have 2 major differing ages of onset. The first group has a young onset, female predominance, and patients frequently are anti-nuclear antibody (ANA) positive and are at risk for iridocyclitis (10). The second group has a later, peripubertal to pubertal onset, also has a female predominance, and may be ANA positive or negative with a very low risk for uveitis. It has been suggested that the age of onset influences long-term outcome (11, 12). Although RF- polyarthritis is second only in frequency of onset type to oligoarthritis, very few studies have focused on the outcome of patients with RF- polyarticular JIA and to our knowledge none that have separated this sub-group by age of onset. Although most studies combine patients with RF- and RF+ polyarticular JIA, it has been assumed by many investigators that the outcome of patients with JIA and older-onset RF- polyarthritis is better outcome than patients with RF+ polyarticular JIA (13). However, to our knowledge, there has not been a large study examining RF- polyarticular JIA with older age of onset.

The aims of this study were to:
1) Determine the outcome of a large cohort of patients with later-onset RF-polyarticular JIA;
2) Determine predictors of outcome at 2 years.

Patients and methods
Patients
The database of the Paediatric Rheumatology Clinic at the Hospital for Sick Children (SickKids) was searched for all patients with a diagnosis of RF-polyarticular JIA seen between the years 1984 and 2002. This search revealed 164 patients aged ≥10 years and <16 years (older-onset) at disease diagnosis. Chart review revealed that 22 patients were incorrectly categorised using the revised ILAR criteria (1) and the charts of 12 patients were unavailable for review. An additional 32 patients were eliminated from the cohort as they were followed for less than 2 years (follow-up time for the study), while 5 more patients were diagnosed at another institution therefore were eliminated as they did not have sufficient data at presentation to meet entry criteria. The study inception cohort therefore consisted of 93 patients with RF- polyarticular JIA diagnosed and followed at the Paediatric Rheumatology Clinic at SickKids for...
Table I. Change of clinical and laboratory features over time.

<table>
<thead>
<tr>
<th>Variable</th>
<th>0 months</th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of active joints</td>
<td>16.0 ± 13.4</td>
<td>9.4 ± 10.3</td>
<td>6.8 ± 9.6</td>
<td>4.7 ± 7.2</td>
</tr>
<tr>
<td>± standard deviation</td>
<td>(n=93)</td>
<td>(n=88)</td>
<td>(n=88)</td>
<td>(n=93)</td>
</tr>
<tr>
<td>Haemoglobin levels (g/L)</td>
<td>125 (92-141)</td>
<td>125 (95-152)</td>
<td>125 (93-149)</td>
<td>125 (99-156)</td>
</tr>
<tr>
<td>median (range)</td>
<td>11/72 (15%)</td>
<td>7/36 (19%)</td>
<td>6/36 (17%)</td>
<td>3/41 (7%)</td>
</tr>
<tr>
<td>number (%) abnormal</td>
<td>125.1 ± 10.8</td>
<td>120.4 ± 23.1</td>
<td>122.8 ± 12.7</td>
<td>128.4 ± 13</td>
</tr>
<tr>
<td>mean ± standard deviation</td>
<td>(n=68)</td>
<td>(n=35)</td>
<td>(n=35)</td>
<td>(n=39)</td>
</tr>
<tr>
<td>White blood cell counts (x10^9/mm³)</td>
<td>7.3 (3.2-131)</td>
<td>6.9 (4.2-16.3)</td>
<td>7.1 (4.8-12.1)</td>
<td>6.6 (3.6-15.3)</td>
</tr>
<tr>
<td>median (range)</td>
<td>11/72 (15%)</td>
<td>4/35 (11%)</td>
<td>5/35 (14%)</td>
<td>6/41 (15%)</td>
</tr>
<tr>
<td>number (%) abnormal</td>
<td>7.6 ± 2.0</td>
<td>7.72 ± 2.5</td>
<td>7.4 ± 1.7</td>
<td>7.2 ± 2.4</td>
</tr>
<tr>
<td>mean ± standard deviation</td>
<td>(n=68)</td>
<td>(n=35)</td>
<td>(n=35)</td>
<td>(n=39)</td>
</tr>
<tr>
<td>Platelet counts (x10^9/mm³)</td>
<td>329 (172-629)</td>
<td>324 (174-540)</td>
<td>313 (159-663)</td>
<td>287 (198-426)</td>
</tr>
<tr>
<td>median (range)</td>
<td>11/72 (15%)</td>
<td>4/35 (11%)</td>
<td>5/35 (14%)</td>
<td>6/41 (15%)</td>
</tr>
<tr>
<td>number (%) abnormal</td>
<td>340 ± 81</td>
<td>333 ± 90</td>
<td>334 ± 106</td>
<td>288 ± 56</td>
</tr>
<tr>
<td>mean ± standard deviation</td>
<td>(n=68)</td>
<td>(n=35)</td>
<td>(n=35)</td>
<td>(n=39)</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>17 (1-114)</td>
<td>17 (1-79)</td>
<td>12 (1-59)</td>
<td>10 (1-90)</td>
</tr>
<tr>
<td>median (range)</td>
<td>33/72 (46%)</td>
<td>6/35 (46%)</td>
<td>12/33 (36%)</td>
<td>6/38 (16%)</td>
</tr>
<tr>
<td>number (%) abnormal</td>
<td>27.1 ± 28.7</td>
<td>19.0 ± 17.6</td>
<td>17.3 ± 16.7</td>
<td>13.8 ± 16.3</td>
</tr>
<tr>
<td>mean ± standard deviation</td>
<td>(n=68)</td>
<td>(n=35)</td>
<td>(n=35)</td>
<td>(n=39)</td>
</tr>
<tr>
<td>Mean CHAQ ± standard deviation</td>
<td>0.75 ± 0.59</td>
<td>0.47 ± 0.51</td>
<td>0.20 ± 0.27</td>
<td>0.26 ± 0.41</td>
</tr>
<tr>
<td>(n=26)</td>
<td>(n=28)</td>
<td>(n=21)</td>
<td>(n=28)</td>
<td></td>
</tr>
<tr>
<td>Patients with a positive ANA</td>
<td>33 (n=70)</td>
<td></td>
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</tbody>
</table>

Patient assessments
The charts of all 93 patients were reviewed and data was collected at the time of diagnosis and every 3 months for a two-year period. The specific data extracted was: height, weight, number of active joints, laboratory measurements, and medications. An active joint was defined as either one that was effused, or had joint line tenderness, pain on motion and limited range of motion. Laboratory measurements included: haemoglobin, white blood cell (WBC) and platelet counts, erythrocyte sedimentation rate (ESR), RF and ANA (positive if titre ≥1:40). Beginning in 1995 Childhood Health Assessment Questionnaire (CHAQ) (14) scores were recorded for each visit (when available). Cumulative joint count was assessed by recording all newly active joints at either presentation, 6, 12, or 24 months. Symmetric arthritis was defined as present if the number of affected joint pairs (if a pair was involved then this was recorded as 2 in the denominator) divided by the total number of joints involved was ≥50%. The following 11 joint pairs were used: shoulders, elbows, wrists, any metacarpophalangeal (MCP) joint involvement (number or location did not need to match), any proximal interphalangeal (PIP) joint involvement of the hand (number or location did not need to match), hips, knees, ankles, any metatarsophalangeal (MTP) joint involvement (number or location did not need to match) of the foot, any PIP joint involvement (number or location did not need to match) of the foot, and the temporomandibular joint (TMJ). These definitions have been used in our previous studies (15). For outcome analyses patients were divided into 5 groups based on the number of active joints: a) Inactive disease: This refers to patients with a joint count of zero but they may be on medication. As we did not have a physician global assessment we were unable to use the Wallace criteria for inactive disease (16); b) Mildly Active arthritis: ≤5 active joints; c) Moderately active arthritis (5-10 active joints); d) Significantly active arthritis; (11-20 active joints) and e) Severe arthritis (>20 active joints). At the time of presentation medication use was recorded but was considered significant only if the patient was taking the medication for a period longer than 3 months.

Statistics
Predictive analysis was performed, using ANOVA, to determine if the number of active joints at 2 years or cumulative joint count at 2 years correlated with the any of the following variables: number of initially active joints (divided into ‘mildly active’, ‘moderately active’ and ‘significantly active’ as defined above) at presentation, age at diagnosis, haemoglobin, white blood cell count, platelet count, ESR, and CHAQ scores. Statistical analysis was generated using SAS software.

Results
Patient characteristics at presentation
The majority of the 93 patients were female with a ratio of 4:1 and a mean age of 12.7±1.8 years at presentation. The mean number of active joints at presentation was 16±13.4 joints with moderately active disease present in 46 patients (50%), 22 significantly active disease (24%) and severe disease in 25 (27%) (Table I, Fig. 1). The most commonly affected joints were the small joints of the hand (MCP, PIP) (67%) and knee (63%) (Table II). Symmetric arthritis was seen in 65% of patients. The mean CHAQ was 0.75±0.59 but was only available in minority of patients (n=26).

The mean haemoglobin, white blood cell counts (WBC) and platelet counts were normal while the mean ESR was mildly elevated (Table I). The ANA was positive in 47% of patients. HLA-B27 was not routinely measured in this cohort.

Outcome
Joint count over time
At 6 months approximately 50% of all patients had less than 5 active joints. This trend for decreasing joint counts continued over time and at 24 months approximately 65% of patients had <5 active joints, and an additional 20% had ≥5 and ≤10. Only 13% of patients had >10 active joints at the end of 2 years as compared to 50% at presentation (Fig. 1).

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Overall 88% of the patients had improved in their joint count category with mean improvement in active joint count of 11.2±13.6 joints. These improvements occurred as early as 6 months with 84% having an improved joint at the 6-month visit. Sixty-one patients (65%) had <5 active joints at 2 years. 

1) Initial moderately active group: Only 4% had a higher joint count at last follow-up at year 2 than at presentation and only 19% of the 46 patients in this group worsened at any time over the 2-year time span. At 24 months the mean improvement of active joints in this group was 3.5±6.3 joints; 46% of patients had inactive disease.

2) Initial significantly active group: Nineteen of the 22 (86%) patients had improvement in their joint count of sufficient magnitude to decrease their category to <5 active joints and 3 were in this category at 2 years (2 remained in this category and only one changed to the higher category of severe-4.6% of total cohort). At 24 months the mean improvement in active joint count was 9.4±7.3 joints; 55% of patients had inactive disease.

3) Initial severe group: Although the severe group had proportionally the most patients with more than 5 active joints at the end of 2 years, 13/25 patients (52%) had <5 active joints at 2-year follow-up and only 3 (12%) remained in the severe category. At 24 months the mean improvement in active joint count was 2±15 joints; 40% of patients had inactive disease.

Laboratory

The mean ESR decreased and was normal by 6 months and remained normal throughout the follow-up period. The mean haemoglobin, white blood cell counts and platelet counts remained normal throughout the study. CHAQ scores improved in the first 12 months and then remained at a low level (0.26±0.41) (Table I).

Treatment

The most commonly prescribed medication was a non-steroidal anti-inflammatory drug (NSAID) (Table III). Only 56% of patients received a disease-modifying anti-rheumatic drug (DMARD) during the study period with the majority of these patients (85%) remaining on a DMARD at the last follow-up at 2 years. The mean time to initiation of DMARD treatment was 5.5 months. A minority of patients were treated with more than one DMARD (14% of patients). Aside from gold salts, the choice of DMARD generally did not change over the study period. Twenty-four percent of patients received oral corticosteroid at some point during the study period and 16% received at least one intra-articular corticosteroid injection. None of the 12% of patients on oral corticosteroid at the 2-year follow were on corticosteroids throughout the study. Only two patients received an anti-tumour necrosis-alpha (anti-TNF-α) agent, or any biologic
agent, and it was successfully stopped prior to the end of the 2-year period without disease flare in both patients. To better understand how initial joint count influenced therapy at last follow-up at 2 years, we looked at which medications the patients were taking at last follow-up according to number of active joints at presentation.

1) Moderately active group:
At last follow-up 21/46 (46%) patients had inactive disease with 8 (17%) of these patients off all medications. Overall, 34 (74%) were on a NSAID; 16 (35%) were on a DMARD (methotrexate in 6 and gold salts in 5); 6 (13%) were on prednisone; and none were on a biologic.

2) Significantly active group:
Twelve of the 22 (55%) patients had inactive disease with 2 (9%) off all medication. Overall, 15 (68%) were on a NSAID; 11 (50%) were on a DMARD (methotrexate in 8); 1 (5%) patients was on prednisone; and none were on a biologic.

3) Severe group:
Ten of the 25 (40%) of patients had inactive disease with 2 (8%) off all treatment. Overall, 17 (68%) were on a DMARD (methotrexate in 16 and hydroxychloroquine in 1); 4 (16%) were on prednisone; 20 were on a NSAID, and none were on a biologic. Of the 13 patients (52%) in this group with <5 joints active at 2 years: 2 were off all medication; 5 were on a NSAID only; 5 were taking a DMARD (all methotrexate); and 1 was on prednisone only.

Table III. Treatment over time and at last follow-up.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Any time (min. 3 months)</th>
<th>At 2-year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-steroid anti-inflammatory medications</td>
<td>98%</td>
<td>74%</td>
</tr>
<tr>
<td>Corticosteroids (any)</td>
<td>34%*</td>
<td>12%*</td>
</tr>
<tr>
<td>Prednisone</td>
<td>24%*</td>
<td>12%*</td>
</tr>
<tr>
<td>Intra-venous methylprednisolone</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Intra-articular</td>
<td>16%</td>
<td>0%</td>
</tr>
<tr>
<td>Disease modifying anti-rheumatic drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>56%</td>
<td>47%</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>36%</td>
<td>32%</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Gold</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Biologics</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Infliximab</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Uveitis
All patients had routine ophthalmological examination and only 2 patients were documented to have had uveitis during the follow-up period. The uveitis in both patients was classified as mild and it was in remission off medication at 2-year follow-up in both.

Predictors of final joint count and cumulative joint count
The only statistically significant associations we found was the correlation between the initial active joint count with both number of active joints at 2 years (r=0.33; p<0.05) and cumulative joint count (r=0.76; p<0.0001). We did not find any correlation of the number of active joints or cumulative joint count at 2 years with age at onset, initial CHAQ, presence or absence of symmetry, wrist or ankle involvement or any of the initial laboratory parameters (including ANA positivity).

Discussion
JIA is a heterogeneous illness with 7 major subtypes each with its own clinical features and prognosis. To date most outcome studies have focused on patients with oligoarticular arthritis, SJIA, psoriatic arthritis, ERA or JIA as a whole. This study is the first that has focused entirely on the outcome of patients with older-onset RF- polyarticular JIA in order to determine if there is an unique subset of JIA. We found that overall this group of patients had a good outcome over a 2-year period. As early as 6 months after initial presentation almost half of the patients had less than 5 active joints and by 24 months 47% had inactive disease and 65% of all patients had <5 active joints, regardless of how many active joints they had at presentation.

The number and persistence of active arthritis is important in determining long-term outcome (17). We found that the majority of all patients had minimally active disease (<5 active joints) after 2 years of follow-up with inactive on medication in 34% of patients and off medication in 13%. This compares to a 2010 report by Albers et al. that reported that 60% of patients with RF- polyarticular JIA (all ages) had at least one period of time in remission in the first 2 years but there was no comment on remission or inactive disease at last follow-up or medication use (18). We found significant changes in joint count occurred within 6 months of diagnosis and only a small percentage (13%) of patients had >10 active joints at 2 years. There were significant changes in the function as measured by the CHAQ as the mean CHAQ decreased from 0.75 at first visit to 0.26 at 2 years; this is greater than the minimal clinically important CHAQ change of 0.13 (19, 20). The development of inactive arthritis and low joint count early, as seen in our study, is important as it has been shown that at least one episode of inactive arthritis within the first 5 years is associated with less long-term joint damage and a better functional outcome than that found in patients who never achieved this state over the same time period (21). Recent large prospective studies have shown that the number of active joints and physical function at presentation is a good predictor of outcome within the first year of disease regardless of JIA onset type (4, 5). In addition, long-term radiologic damage has been associated with duration of active disease (11) and it has been proposed that the time with inactive disease in the first 2 years can be used as a predictor of disease activity in the next 3 years (18). It is difficult to compare our results to other studies as these studies have always combined patients with both ages of onset of RF-polyarticular JIA, many studies combined RF- and RF+ polyarticular JIA patients and the follow-up times are different (3-5, 13, 22, 23). Longer-term follow-up and radiographic studies will be required to confirm the 5 and 10 year outcome of this sub-group of patients as it has been shown that up to 50% may experience a relapse off medication (24).

The long-term outcome of JIA has significantly improved since the first descriptions in the early 1970s (25, 26). The initial improvement in polyarticular course JIA was associated with the use of methotrexate and other DMARDs while the more recent improvement is associated with the use of biologics in patients who have failed DMARD (27, 28). In our study only 56% of the patients received a DMARD during their disease course and 47% were on a DMARD at last-follow-up (35% patients in the initial group of patients with moderately active arthritis group, 50% in significantly active group and 68% in the severe arthritis group). This percentage of patients having received a DMARD is lower than previously reported in patients with RF- polyarticular JIA and in studies that combined patients with RF- and RF+ polyarticular JIA (13, 22, 29). Only 2 patients were treated with a biologic agent and none were still receiving this therapy at 2 years. However, most of the patients in this study were seen prior to the use of biologics and it is likely that more patients would have been treated with this therapy and some may have been on this treatment at 2 years. Therefore, despite the use of biologics in <3% of patients, only 3 patients (13%) had >10 active joints and 20% of patients had >5 and <10 active joints, at last follow-up suggesting that approximately 25% of patients with late-onset RF- polyarticular JIA would be considered for treatment with a biologic based on active joint at 24 months.

It is important to determine if there are any clinical and laboratory features associated with good and/or poor outcome. We found that there was a significant correlation between initial number of active joints and both final joint count and cumulative joint count but not wrist or ankle involvement or symmetry as had been previously suggested in patients with an oligoarticular onset of JIA and/or response to methotrexate at 6 months (30-32). Although patients with higher initial joints were the most likely group to have a high final joint counts, approximately half of the patients who presented with >20 active joints had <5 active joints at 2 years following diagnosis. We did not find any statistically significant correlation of routinely measured laboratory variable including ANA status with cumulative joint count over the course of the disease. These results suggest that only initial joint count but not laboratory investigation predicted long-term
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PAEDIATRIC RHEUMATOLOGY