Magnetic resonance imaging in juvenile idiopathic arthritis diagnosis and follow-up, beyond imagination
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Chapter 2

Frequency of joint involvement in juvenile idiopathic arthritis during a 5-year follow-up of newly diagnosed patients: implications for MR imaging as outcome measure

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Submitted
Abstract

Objectives
To assess the sequence and type of active joints in a cohort of newly diagnosed juvenile idiopathic arthritis (JIA) patients with full access to current treatment at first visit and during a follow-up period of 5-years, in order to identify an index joint/group of joints for MRI in JIA.

Methods
Patient charts of all consecutive newly diagnosed JIA patients with a follow-up duration of at least 5 years were analyzed. Patients were derived from two tertiary pediatric rheumatology centers. Patient characteristics and data concerning the presence of joints with arthritis and the use of medication were recorded.

Results
Findings from 95 JIA patients (40 [42%] oligoarticular and 45 [43%] polyarticular) were analyzed. At first visit, distribution of active joints among patients was as follows: knee (n = 70, 74%), ankle (n = 55, 58%), elbow (n = 23, 24%), wrist (n = 23, 24%), metacarpo-phalangeal [MCP] (n = 20, 21%), proximal-interphalangeal [PIP] (n = 13, 14%), hip (n = 6, 6%), shoulder (n = 5, 5%), and distal-interphalangeal [DIP] (n = 4, 4%) joints. After a follow-up period of 5 years, the cumulative percentage of patients with specific joint involvement changed into: knee (n = 88, 93%), ankle (n = 79, 83%), elbow (n = 43, 45%), wrist (n = 38, 40%), MCP (n = 36, 38%), PIP (n = 29, 31%), shoulder (n = 20, 21%), hip (n = 17, 19%), and DIP (n = 9, 10%) joints.

Conclusions
Despite changes in treatment strategies over the years, the knee remains the most commonly involved joint at onset and during follow-up in JIA, followed by the ankle, elbow and wrist. For the evaluation of outcome with MRI the knee appears the most appropriate joint in JIA.
Introduction

The umbrella term juvenile idiopathic arthritis (JIA) covers a group of heterogeneous conditions that encompass all forms of arthritis of unknown etiology and pathophysiology which begin before the age of 16 years and persist for more than six weeks (1). Studies in developed countries reported a prevalence that varies between 16 and 150 per 100,000 (2, 3). The JIA entity is characterized by prolonged synovial inflammation that can lead to destruction of joints, pain and loss of function (2).

Early therapeutic interventions improve long-term outcome. Therefore objective and accurate measures in the assessment of disease activity are needed for the evaluation of individual response to therapy and general efficacy of treatment in JIA (4, 5). To date, magnetic resonance imaging (MRI) is considered to be the most suitable imaging modality in this respect, as advances in MRI techniques have substantially improved evaluation of joint pathologies in JIA. Although there is fair strength of evidence that MRI is an accurate diagnostic method for evaluating synovium and cartilage and for assessing clinical responsiveness to treatment in peripheral joints in JIA (6, 7), currently there is no evidence supporting imaging of a specific joint within the scope of clinical trials. The performance of an MRI examination for assessment of more than one or two joints/group of joints has limitations because of time constraints and, thereby, reduces feasibility of MRI in children with JIA. Therefore, it is important to identify an index joint, and in that way increase the value of MRI as an outcome measure for research in JIA.

An index joint can be defined as the joint that is representative of the overall burden of the disease. One important aspect is that it should be a clinically frequently involved joint, with respect to presence of clinical arthritis, and thereby enclose most of the JIA patients. Such a joint has already been identified in adult rheumatoid arthritis patients concerning MRI research outcomes (e.g. the wrist) (8), but this information is lacking for JIA patients. Although there is literature on the diverse pattern of disease course and disease outcome in JIA (9), there are - to the best of our knowledge - no data available regarding the long-term distribution and course of the disease in specific joints in children with JIA. Therefore, the aim of our study was to assess the sequence and type of active joints in a cohort of newly diagnosed JIA patients with full access to current treatment at first visit and during a follow-up period of 5-years, in order to identify an index joint/group of joints for MR imaging in JIA.
Materials and methods

Patients

This study was performed in accordance with the declaration of Helsinki and the local medical ethical regulations. The requirement for informed consent was waived by the institutional review board. Data of all consecutive patients visiting the outpatient clinics of two tertiary pediatric rheumatology centers between January 2002 and January 2007 were identified in the electronic hospital administration system and retrospectively analyzed. Patients fulfilling the following criteria were included: a confirmed diagnosis of JIA according the International League of Associations for Rheumatology (ILAR) criteria for JIA (1); age between 0 and 16 years at the first visit; and a regular follow-up (defined as 2 or more outpatient clinic visits per year) for at least 5 years. All patient charts were reviewed by one person.

For eligible patients, data regarding the presence of joint involvement throughout the follow-up and use of medication were recorded. Collected data included age at the first visit, gender, date of disease onset, date of diagnosis, subtype of JIA, presence of joints with clinical arthritis as judged by the pediatric rheumatologists (temporomandibular joint (TMJ), shoulder, elbow, wrist, metacarpophalangeal joint (MCP), proximal interphalangeal joint (PIP), distal interphalangeal joint (DIP), sacroiliac joint (SI), hip, knee, ankle, cervical spine, thoracic spine, lumbar spine), used medication after the first visit (no medication, NSAID, prednisone, methotrexate, sulfasalazine, tumor necrosis factor-α (TNF-α) blockers, other DMARD).

At both sites, the standard clinical assessment includes a 67-joint count for assessing clinical actively inflamed joints. Actively inflamed joints were defined as joints with swelling as well as joints with tenderness or pain on motion and limited range of motion (1, 10). The number and type of actively inflamed joints were documented in the patient chart by the pediatric rheumatologist. Depending on the pediatric rheumatologist, joint findings were marked on a homunculus or systematically described in words.

Changes during the follow-up period, with respect to joints with arthritis and use of anti-rheumatic medication, were collected. Joints with questionable or equivocal joint findings were considered to be not actively inflamed; the definition of clinically active joints was strictly maintained. Patient charts with incomplete or missing data concerning physical examination findings were excluded.
Statistics
Descriptive statistics were reported in terms of medians and inter-quartile ranges (IQR) for the continuous variables and in terms of absolute frequencies and percentages for the categorical variables. The Fisher’s exact test and Mann-Whitney U test were used to analyze differences between groups. A P value of less than 0.05 indicated a statistically significant difference. All data were analyzed by using SPSS version 18.0 (SPSS, Chicago, ILL, USA).

Results
Patients
As shown in Figure 1, the electronic hospital administration system identified 316 patients visiting the outpatient clinics of the two tertiary pediatric rheumatology centers between 2002 and 2006. Patients not fulfilling the ILAR criteria for JIA, patients without a regular follow-up of at least 5 years, and patients with missing data were excluded (Figure 1). Therefore, data from 95 (66.3% female) newly diagnosed JIA patients with a mean age at first visit of 9.0 years (SD 4.8) could be included for the purpose of this study. Patient characteristics are shown in Table 1. Depending on the disease severity as judged by the pediatric rheumatologist, the number of visits varied between two and eight times a year.

Table 1. Patient characteristics of 95 newly diagnosed JIA patients at baseline

<table>
<thead>
<tr>
<th>All patients</th>
<th>n = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) of female patients</td>
<td>63 (66.3)</td>
</tr>
<tr>
<td>Age at study visit, mean years (SD)</td>
<td>9.0 (4.8)</td>
</tr>
<tr>
<td>Disease duration at first visit, median months (IQR)</td>
<td>6 (3 – 16)</td>
</tr>
<tr>
<td>JIA category, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Systemic arthritis</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Persistent oligoarthritis</td>
<td>27 (28.4)</td>
</tr>
<tr>
<td>Extended oligoarthritis</td>
<td>13 (13.7)</td>
</tr>
<tr>
<td>Polyarthritis RF-negative</td>
<td>39 (41.1)</td>
</tr>
<tr>
<td>Polyarthritis RF-positive</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Enthesitis related arthritis (ERA)</td>
<td>8 (8.4)</td>
</tr>
<tr>
<td>Psoriatic arthritis*</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Undifferentiated JIA</td>
<td>2 (2.1)</td>
</tr>
</tbody>
</table>

* Two patients had poly-articular onset
Joint involvement
At first visit the percentage of patients with arthritis of the following joints were noted: knee \((n = 70, 74\%)\), ankle \((n = 55, 58\%)\), elbow \((n = 23, 24\%)\), wrist \((n = 23, 24.2\%)\), MCP \((n = 20, 21\%)\), PIP \((n = 13, 14\%)\), hip \((n = 6, 6\%)\), shoulder \((n = 5, 5\%)\), DIP \((n = 4, 4\%)\), cervical spine
(n = 2, 2%), TMJ (n = 2, 2%), SI (n = 1, 1%), lumbar spine (n = 1, 1%), and thoracic spine (n = 0, 0%). Joint involvement during a follow-up period of 5 years of the most informative joints is depicted in Figure 2. The cumulative frequency of joint involvement after a follow-up period of 5 years was: knee (n = 88, 93%), ankle (n = 79, 83%), elbow (n = 43, 45%), wrist (n = 38, 40%), MCP (n = 36, 38%), PIP (n = 29, 31%), shoulder (n = 20, 21%), hip (n = 17, 19%), DIP (n = 9, 10%), cervical spine (n = 8, 8%), TMJ (n = 6, 6%), SI (n = 4, 4%), lumbar spine (n = 3, 3%), and thoracic spine (n = 0, 0%), as shown in Figure 3.

**Figure 2.** Absolute frequency (percentage) of joint involvement in 95 juvenile idiopathic arthritis patients presenting with clinical activity during a follow-up period of 5 years.

**Figure 3.** Cumulative frequency (percentage) of 95 juvenile idiopathic arthritis patients presenting with clinical activity during a follow-up period of 5 years.
Persistent-oligoarticular versus polyarticular onset JIA patients

Polyarticular onset was observed in 43 (45%) JIA patients; RF-negative \( n = 39 \), RF-positive polyarthritis \( n = 2 \), and psoriatic arthritis \( n = 2 \). No polyarticular onset was observed in the systemic arthritis, undifferentiated, or enthesitis related arthritis JIA subgroups. Therefore, we included 27 (28%) persistent-oligoarticular and 43 (45%) polyarticular onset JIA patients. No statistical significant differences were detected between the persistent-oligoarticular and polyarticular onset JIA patients with respect to age, gender, and disease duration. At the first visit frequency of joint involvement between persistent-oligo and polyarticular onset JIA patients differed significantly with respect to the elbow (\( n = 2 \) [7%] vs. \( n = 18 \) [42%]; \( P = 0.002 \)), MCP (\( n = 0 \) [0%] vs. \( n = 16 \) [37%]; \( P < 0.001 \)), PIP (\( n = 0 \) [0%] vs. \( n = 9 \) [21%]; \( P = 0.010 \)), and ankle (\( n = 9 \) [33%] vs. \( n = 31 \) [72%], respectively; \( P = 0.003 \)). No such differences were found regarding the other joints, including the wrist (\( n = 5 \) [19%] vs. \( n = 14 \) [33%]; \( P = 0.272 \)), and knee (\( n = 20 \) [74%] vs. \( n = 33 \) [77%], respectively; \( P = 1.0 \)). Changes in frequency of joint involvement in persistent-oligoarticular and polyarticular onset JIA patients during a 5-year follow-up period are depicted in Figure 4.

Marked differences with respect to the cumulative frequency of joint involvement in persistent-oligoarticular and polyarticular onset JIA patients with clinical arthritis after a follow-up period of 5 years were noted in the shoulder (\( n = 3 \) [11%] vs. \( n = 16 \) [37%]; \( P = 0.026 \)), elbow (\( n = 7 \) [26%] vs. \( n = 27 \) [63%]; \( P = 0.003 \)), wrist (\( n = 6 \) [22%] vs. \( n = 22 \) [51%]; \( P = 0.024 \)), MCP (\( n = 1 \) [4%] vs. \( n = 24 \) [56%]; \( P < 0.001 \)), PIP (\( n = 1 \) [4%] vs. \( n = 20 \) [47%]; \( P < 0.001 \)), hip (\( n = 2 \) [7%] vs. \( n = 14 \) [33%]; \( P = 0.019 \)), and ankle (\( n = 16 \) [59%] vs. \( n = 42 \) [98%], respectively; \( P < 0.001 \)). Joint involvement of the knee (\( n = 24 \) [89%] vs. \( n = 42 \) [98%], respectively; \( P = 0.291 \)) were comparable between the persistent oligoarticular and polyarticular-onset JIA patients.
**Medication**

NSAIDs were the most commonly used drugs after the first visit used by 84 (88%) patients. The cumulative frequency of JIA patients using NSAIDs was 94 (99%). Methotrexate was started by 14 (15%) patients after the first visit, though after a follow-up period of 5 years the cumulative frequency of patients using MTX was 74 (78%). No TNF-α blockers were prescribed during the first half-year after diagnosis for any of the evaluated patients, and the cumulative frequency of patients using TNF-α blockers was 25 (26%) at the end of the 5-year follow-up period.

**Discussion**

This paper reports the frequency of joint involvement in different JIA subtypes in patients with full access to current treatment during a total follow-up duration of 5 years in order to get insight towards the sequence of joint involvement over time, with the aim of identifying index joints in JIA for MR imaging. Our study shows differences with respect to the presence of arthritis between different joints and between patients with different subtypes of JIA (persistent-oligoarticular vs. polyarticular onset). In our series the knee was the most commonly involved joint, as clinically evaluated at the first visit (up to 77% of cases) and during a follow-up period of 5 years (up to 98% of cases), followed by the ankle, elbow and wrist.

In our study the most significant changes with respect to the frequency of joint involvement in patients with arthritis were noted during the first year of follow-up after the first clinic visit. An increase in the absolute frequency of joint involvement was observed during the first six months concerning all joints, consequently these frequencies decreased. This is in line with the results of Albers et al., who found that the time of disease activity significantly decreases during the first two years after the diagnosis of JIA (11). Although the frequency of joints with arthritis decreased over time (during a follow-up period of 5 years), in our study population a major percentage of the JIA patients still showed arthritis at the 5-year final follow-up time point. This is consistent with the results of Oen et al., who found that clinically active JIA often continues to be present for several years after the initial diagnosis and most often extends into adulthood (12, 13). Although JIA patients with predominant wrist involvement have been reported to show poor therapy response and a destructive course of the disease (5, 14), in our study only a relatively small subgroup of the JIA population presented with wrist involvement at the first visit (n = 23, 24%). Even after a follow-up period of 5 years, the cumulative frequency of polyarticular onset JIA patients with wrist involvement remained relatively low (n = 22, 51%), as compared to the...
cumulative frequency of JIA patients who presented with knee involvement, which increased up to 98% in the polyarticular onset JIA subgroup.

The number of patients with clinical signs of temporomandibular joint arthritis was low in our study. Other studies have shown that TMJ involvement commonly occurs in JIA patients, but their symptoms are typically subtle and can therefore be easily missed (15, 16). MRI of the TMJ has increased the awareness of TMJ arthritis, and MRI follow-up of the TMJ may reflect changes in disease activity as a result of treatment (17).

To date, the evaluation of disease activity both in daily practice as well as in clinical trials is based on physical examination (18, 19), which has, even by experienced observers, only limited reliability (20). Advances in therapies have increased the number of patients reaching clinical inactive disease, which cannot always be reliably demonstrated by physical examination alone (19, 21, 22). Within the past decade, the use of MRI and advances in MRI techniques have substantially improved the evaluation of joint pathologies in JIA. MRI is considered to be the most sensitive imaging tool for the detection of (subclinical) synovitis, as well as for the detection of cartilage lesions and bone erosions (6, 23).

Limitations of our study should be considered. The retrospective cohort design might have resulted in missing data. Although some information of this study requires confirmation in larger studies, such as the relatively low frequency of involvement of wrists and TMJs in this study, our results are representative for the frequency of joint involvement in JIA patients visiting referral pediatric rheumatology centers. Furthermore, our results should be interpreted cautiously with respect to some of the JIA subtypes given their small sample size. This might hamper the generalizability of our study findings for the complete JIA population.

Despite the continuous implementation of modern imaging techniques there is a lack of consensus on clinical attributes that should be considered in the assessment of JIA patients. Knowledge on such clinical attributes for instance expected frequency and sequence of joint involvement in JIA in association with standardization of imaging protocols will enable the development of MRI scores for assessment of JIA prioritizing target joints. Such scoring systems are urgently needed both in clinical practice and in the conduct of clinical trials. Without knowledge of these clinical attributes it becomes challenging if ever possible to develop and validate more objective and accurate measures for evaluation of individual response to therapy and efficacy of treatment.
In this study we concluded that upon clinical assessment the knee is the most commonly affected joint in JIA both at the first visit and during a follow-up period of 5 years, followed by the ankle, elbow and wrist. We also demonstrated that the involvement of the shoulder, elbow, MCP, PIP, hip and ankle joints differs between persistent-oligoarticular and polyarticular onset JIA patients. This study helps to determine the index joints / groups of index joints for MR imaging in JIA which can be useful in the development of MRI assessment scores targeted to specific joints within the scope of future clinical trials. According to our results the knee is the clinically most frequently involved joint in JIA and can, therefore, be considered as the most appropriate joint to be used as outcome for MR imaging research.
References


