Magnetic resonance imaging in juvenile idiopathic arthritis diagnosis and follow-up, beyond imagination
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Citation for published version (APA):
Hemke, R. (2013). Magnetic resonance imaging in juvenile idiopathic arthritis diagnosis and follow-up, beyond imagination

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Chapter 6

Contrast-enhanced MRI compared with the physical examination in the evaluation of disease activity in juvenile idiopathic arthritis

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Accepted for publication in European Radiology
Abstract

Objective
To assess the value of MRI in discriminating active and inactive JIA patients and to evaluate the diagnostic performance of MRI compared with physical examination in the assessment of disease status in JIA patients

Methods
Consecutive JIA patients with knee involvement were prospectively studied using an open-bore MRI. Patients were classified as clinically active or inactive. MRI-features were evaluated using the JAMRIS system, comprising validated scores for synovial hypertrophy, bone marrow edema, cartilage lesions and bone erosions.

Results
Imaging findings from 146 JIA patients were analyzed (59.6% female, mean age 12.9 years). The inter-reader reliability was good for all MRI-features (ICC = 0.87-0.94). No differences were found between both groups regarding MRI-scores of bone marrow edema, cartilage lesions or bone erosions. Synovial hypertrophy scores differed significantly between groups ($P = 0.016$). Nonetheless, synovial hypertrophy was also present in 14 JIA patients (35.9%) with clinically inactive disease. Of JIA patients considered to be clinically active, 48.6% showed no signs of MRI-based synovitis.

Conclusions
MRI is able to discriminate clinically active and inactive JIA patients. However, the physical examination is neither very sensitive nor specific in the evaluation of JIA disease activity. Subclinical synovitis was present in more than 35% of presumed clinically inactive patients.
Introduction

Synovitis is the most critical hallmark of disease activity in juvenile idiopathic arthritis (JIA) (1-3). Longitudinal studies concerning inactive rheumatoid arthritis (RA) patients showed that subclinical synovitis upon MRI is associated with progressive radiographic damage (4). Until now the physical examination has been considered the gold standard for the evaluation of JIA disease activity in both daily practice as well as in clinical trials. Though, it was shown to be of limited reliability, even when performed by an experienced observer (5).

In JIA, magnetic resonance imaging (MRI) is considered to be the most sensitive imaging modality for the assessment of synovitis (6-8). Furthermore, MRI is more sensitive in the detection of destructive changes of cartilage and bone compared to conventional radiography and ultrasonography (7-9). Experience on the use of MRI in the assessment of JIA is limited. Hence, this technique is under-utilized both in clinical practice and research. Part of the reason for the under-utilization of MRI as an outcome measure in clinical trials of JIA relates to the lack of knowledge on its discriminative value. To be useful as an outcome measure in clinical trials and daily practice, a measure should be able to discriminate groups of interest. Moreover, no prospective studies have been performed comparing contrast-enhanced MRI and the physical examination in the assessment of JIA disease activity of the knee. Therefore, the aim of our study was to assess the value of MRI in discriminating clinically active and inactive JIA patients and to evaluate the diagnostic performance of MRI compared with physical examination in the assessment of disease status of knees in JIA patients.

Materials and Methods

Patients

All consecutive patients with MRI evaluation of the knee between January 2009 and January 2012 were included in this prospective study. Patients visited one of the outpatient clinics of two tertiary pediatric rheumatology centers. At time of presentation all patients underwent clinical and laboratory assessments, followed by contrast-enhanced MRI. Inclusion criteria were clinical active arthritis (Active JIA; newly diagnosed JIA or relapsing/remitting disease), or follow-up of JIA patients with clinically inactive disease and a history of clinical evident arthritis in at least one knee (Inactive JIA). All patients fulfilled the international league of associations for rheumatology (ILAR) criteria for JIA, defined as an arthritis of unknown etiology that begins before the age of
16 and persists for at least 6 weeks (10). Clinically inactive patients met the preliminary criteria for inactive disease in JIA as described by Wallace et al (11). For ILAR classification, all new patients were clinically evaluated and reclassified if necessary after a period of 6 months. Exclusion criteria were: a history of intra-articular corticosteroid injection within the last six months, the need for anesthesia during the MRI examination, and general contraindications for MRI. This study was performed in accordance with the declaration of Helsinki and the local medical ethical regulations. Written informed consent was obtained from at least one parent of each child.

Clinical assessment
Physical examination was performed by the same experienced pediatric rheumatologists during the research period. The clinical assessment consisted of a 67-joint count defining the presence of swelling, pain on motion/tenderness and limited range of motion. A physician's global assessment of disease activity, a patient's global assessment of well-being and an assessment of patient's pain were all measured on a 100 mm visual analogue scale (VAS). The Dutch version of the childhood health assessment questionnaire (CHAQ) was used to evaluate functional ability (12, 13). Laboratory tests included the erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) level. In addition – to evaluate the clinically active JIA group in more detail – overall disease activity was judged by the treating pediatric rheumatologist using a five-point scale comprising: (inactive), minimally active, mildly active, moderately active, and severely active.

MRI protocol
To increase feasibility, MR images from all patients were obtained using an open-bore 1.0-T magnet and a dedicated knee coil (Panorama HFO, Philips Medical Systems, Best, the Netherlands) (14). No sedation was used. The children were placed in the supine position with the knee joint centrally in the magnetic field. Contrast-enhanced MRI of the clinical most involved knee (target joint) was performed. In case of clinically inactive disease, the former most affected knee was considered to be the target joint. If there were no differences in clinical activity between knees, the right knee was considered to be the target joint. MRI sequences included sagittal T2-weighted fat saturated images (TR 2800-4500 ms; TE 50 ms; slice thickness 4 mm; field of view 150 × 150 mm; matrix 300 × 242), coronal T2-weighted fat saturated images (TR 2800-4500 ms; TE 50 ms; slice thickness 4 mm; field of view 150 × 150 mm; matrix 300 × 247), axial T2-weighted fat saturated images (TR 2800-4500 ms; TE 50 ms; slice thickness 4 mm; field of view 150 × 150 mm; matrix 300 × 270), sagittal T1-weighted images obtained before and after intravenous contrast (0.1 mmol per kilogram of body weight, gadobutrol, Bayer healthcare, Berlin, Germany) injection (TR 450-650 ms; TE 10 ms; slice thickness 4 mm; field of view 150 × 150 mm; matrix 300 × 248),
and axial T1-weighted fat saturated images obtained after intravenous contrast injection (TR 400-750 ms; TE 10 ms; slice thickness 4 mm; field of view 150 × 150 mm; matrix 272 × 192).

Image analysis
The image sets were scored by a radiology trainee (RH, 5 years of experience in musculoskeletal radiology) blinded to clinical history, including the duration, extent, and severity of the symptoms. To evaluate the inter-observer reliability, a random sample survey was taken of 60 MRI data sets. These MR images were scored independently by an expert musculoskeletal radiologist (MM, 17 years of experience in musculoskeletal radiology), also blinded to clinical history, including the duration, extent, and severity of the symptoms. The MR images were scored in accordance with the Juvenile Arthritis MRI Scoring (JAMRIS) system. This scoring method has been validated and described before in detail (15).

Statistics
Descriptive statistics were reported in terms of percentages, means, medians, ranges, inter-quartile ranges and standard deviations. The independent samples T-test, Fischer’s exact test, and the Mann-Whitney U test were used to analyze differences between groups. All tests assumed a two-tailed probability and a P value of less than 0.05 indicated a statistical significant difference. Correlations were assessed using the Spearman’s rank correlation coefficient ($R_s$), and was classified as follows: $R_s < 0.40 = \text{poor}$, $0.40 - 0.60 = \text{moderate}$, $0.60 - 0.80 = \text{substantial}$, and $>0.80 = \text{good correlation}$. The single measure intraclass correlation coefficient (ICC) was used to analyze reliability, and was classified as follows: ICC $<0.40 = \text{poor}$, $0.40 - 0.60 = \text{moderate}$, $0.60 - 0.80 = \text{substantial}$, and $>0.80 = \text{good reliability}$. All data were analyzed by using SPSS version 19.0 (SPSS, Chicago, ILL, USA).

Results
Patients
In this 3-year prospective study on imaging, MRI data sets of 171 consecutive patients suspected and/or diagnosed with arthritis of the knee were collected. Twenty-five (14.6%) patients were excluded: one was diagnosed with reactive knee symptoms due to bilateral discoid menisci, two were diagnosed with osteochondritis dissecans, one was diagnosed with a rupture of the meniscus, one scan was excluded due to technical problems, and 20 patients were upon follow-up diagnosed with other non-rheumatologic ailments. Therefore, findings from 146 JIA patients were analyzed.
patients (59.6% female patients) with a mean age of 12.9 years (SD 3.3, min-max 5.3-19.1) were analyzed. Frequency of JIA subtypes were as follows: 39 (26.7%) persistent oligoarthritis, 22 (15.1%) extended oligoarthritis, 59 (40.4%) polyarthritis, 2 (1.4%) systemic onset, 5 (3.4%) psoriatic arthritis, 14 (9.6%) enthesitis-related arthritis, and 5 (3.4%) undifferentiated JIA. Of these patients, a total of 29 (19.9%) patients received no medication, 22 (15.1%) patients used NSAIDs, 79 (54.1%) additional systemic DMARDs, and 16 (11.6%) patients were also treated with a tumor necrosis factor (TNF)-α inhibitor.

To evaluate the discriminative value of MRI, these 146 JIA patients were subdivided based on their clinical overall disease activity. Thus, 39 (26.7%) patients were scored to be clinically inactive, consequently 107 (73.3%) JIA patients were clinically active. Clinically inactive patients had a median duration of clinical inactive disease of 12 months (IQR 7–26 months). Age, gender, and disease duration were comparable between both groups. Disease activity, 67-joint count, and CHAQ scores differed significantly between subgroups. No such differences were found regarding the ESR and CRP level. An overview of the clinical characteristics in both groups is presented in Table 1.

### Table 1. Patient characteristics of 146 JIA patients

<table>
<thead>
<tr>
<th></th>
<th>Inactive</th>
<th></th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 39 (26.7%)</td>
<td>n = 107 (73.3%)</td>
<td></td>
</tr>
<tr>
<td>No. (% of female patients</td>
<td>23 (59.0)</td>
<td>64 (59.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Age at study visit, mean years (SD)</td>
<td>13.1 (3.4)</td>
<td>12.8 (3.3)</td>
<td>0.693</td>
</tr>
<tr>
<td>Disease duration at study visit, years</td>
<td>3.1 (1.9-5.2)</td>
<td>2.8 (0.8-4.6)</td>
<td>0.940</td>
</tr>
<tr>
<td>Physician's global assessment of overall disease activity</td>
<td>0 (0-3)</td>
<td>27 (11-66) &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Patient's global assessment of overall well-being</td>
<td>4 (0-13)</td>
<td>37 (6-59) &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Patient's pain assessment</td>
<td>7 (0-15)</td>
<td>40 (11-66) &lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
| C-HAQ score | 0.000 (0.000-0.500) | 0.875 (0.250-1.500) <0.001 
| No. of active joints | 0 (0-0) | 2 (1-4) <0.001 |
| No. of joints with limited range of motion | 0 (0-1) | 1 (0-2) <0.001 |
| Erythrocyte sedimentation rate, mm/hour | 5 (2-7) | 5 (2-8) 0.349 |
| C-reactive protein level, mg/l | 1 (1-1) | 1 (1-1) 0.643 |

*Except where otherwise indicated, values are median (inter-quartile range)

*P values indicate differences between groups. Except where otherwise indicated, Mann-Whitney U test was used to analyze differences between groups.

*Fisher’s exact test

*Independent samples T-test

*Measured on a 0-100 mm visual analogue scale (0 = best, 100 = worst)

*Units; 0 = best, 3 = worst
Additionally clinically active patients were subdivided based on overall disease activity as judged by the pediatric rheumatologist as follows: 27 (18.5%) patients minimally active, 53 (36.3%) patients mildly active, 21 (14.4%) patients moderately active, and 6 (4.1%) patients were considered to be clinically severely active.

**MRI findings**

Image quality was satisfactory in all patients and all children were able to go through the complete MRI examination. An overview of the JAMRIS scores in the studied groups is presented in Table 2. No significant differences were found between the two groups with respect to bone marrow changes (Figure 1), cartilage lesions, and bone erosions. Synovial hypertrophy scores differed significantly between clinically active and inactive JIA patients ($P = 0.016$), scores tended to be higher in clinically more active patients as compared to clinically less active or inactive JIA patients as shown in Figure 2. Synovial hypertrophy was present in 10 (37.0%) minimally active JIA patients, 26 (49.1%) mildly active patients, 13 (61.9%) moderately active patients, and in 5 (83.3%) severely active patients (Figure 3).

Table 2. Juvenile Arthritis MRI Scoring system (JAMRIS) scores in 146 JIA patients

<table>
<thead>
<tr>
<th>Synovial hypertrophy, mean (min-max)</th>
<th>Inactive ($n = 39$ (26.7%))</th>
<th>Active ($n = 107$ (73.3%))</th>
<th>$P$ value$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow changes, mean (min-max)</td>
<td>0.72 (0-4)</td>
<td>1.79 (0-12)</td>
<td>0.016</td>
</tr>
<tr>
<td>Cartilage lesions, mean (min-max)</td>
<td>0.74 (0-5)</td>
<td>0.79 (0-7)</td>
<td>0.752</td>
</tr>
<tr>
<td>Bone erosions, mean (min-max)</td>
<td>0.00 (0-0)</td>
<td>0.08 (0-2)</td>
<td>0.103</td>
</tr>
</tbody>
</table>

$^b$ $P$ values indicate differences between groups. The Mann-Whitney $U$ test was used to analyze differences between groups.

Figure 1. Coronal fat-saturated T2-weighted images obtained (a) in an 11-year old girl with clinically inactive JIA showing bone marrow changes suggestive of bone marrow edema in the weight bearing region of the medial femur, and (b) a 15-year old boy with clinically active JIA showing bone marrow edema in the lateral condyle of the femur.
Figure 2. Mean synovial hypertrophy scores in 146 JIA patients, subdivided based on overall disease activity.

Figure 3. Presence of MRI features in 146 JIA patients, subdivided based on overall disease activity.
As shown in Table 3, synovial hypertrophy was also present in 14/39 (35.9%) clinically inactive JIA patients (Figure 4). Importantly, disease duration in the past, duration of inactive disease, current disease activity scores, joint scores, CHAQ scores, and blood parameters of inflammation (ESR and CRP) were comparable between inactive patients with and without the presence of synovitis upon MRI. On the other hand, 52/107 (48.6%) JIA patients considered to be clinically active showed no signs of synovial hypertrophy upon MRI.

Table 3. 2x2 table showing presence of MRI based synovitis compared to clinical activity (No. (%))

<table>
<thead>
<tr>
<th>Synovitis upon MRI</th>
<th>Clinically active JIA</th>
<th>Clinically inactive JIA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>55 (37.7%)</td>
<td>14 (9.6%)</td>
</tr>
<tr>
<td>No synovitis upon MRI</td>
<td>52 (35.6%)</td>
<td>25 (17.1%)</td>
</tr>
<tr>
<td></td>
<td>107 (73.3%)</td>
<td>39 (26.7%)</td>
</tr>
</tbody>
</table>

Figure 4. Axial fat-saturated contrast-enhanced T1-weighted images obtained (a) in a 13-year old girl with clinically inactive JIA showing no signs of patellofemoral synovial hypertrophy (score of 0 (<2mm)), and (b) a 11-year old girl with clinically inactive JIA showing, among other locations, presence of patellofemoral synovial hypertrophy (arrows) resulting in a patellofemoral synovial hypertrophy score of 1 (2-4mm).

Correlation between clinical parameters and MRI scores

As shown in Figure 5, synovial hypertrophy scores correlated moderately with the physicians’ global assessment of overall disease activity ($R_s = 0.410, P < 0.001$). No significant correlations were found between one of the clinical parameters and bone marrow change, cartilage lesion or bone erosion scores.

Inter-observer reliability

Reliability was good for all MRI features (ICC 0.85-0.96). Inter-observer reliability was as follows: ICC for synovial hypertrophy 0.93 (95% CI 0.86-0.96), bone marrow changes suggestive for bone marrow edema 0.85 (95% CI 0.76-0.91), cartilage lesions 0.96 (95% CI 0.92-0.98) and bone erosions 0.94 (95% CI 0.88-0.96).
Figure 5. Scatter dot-plot correlating synovial hypertrophy scores with the physicians’ global assessment of overall disease activity ($R_s = 0.410, P < 0.001$).

Discussion

Our study evaluated the value of contrast-enhanced MRI in discriminating clinically active and inactive JIA patients. Furthermore, we evaluated the diagnostic performance of MRI compared to physical examination in the assessment of disease status in JIA patients. MRI proved to be capable differentiating patient groups with clinically active and inactive disease with respect to synovial hypertrophy scores. Subclinical synovitis upon MRI was present in more than one third of the presumed clinically inactive JIA patients.

MRI is the most sensitive imaging tool for the assessment of synovitis, the most important hallmark of disease activity in JIA (7). Even though MRI is superior in assessing disease activity and erosive changes of cartilage and bone (6), its use as an outcome measure in both clinical practice and research is still under-utilized. An important aspect for this under-utilization refers to the lack of data on the discriminative value of MRI. To be helpful as an outcome measure in every day practice and clinical trials, an imaging measure must be able to discriminate groups of interest. The results of our current study show that the JAMRIS synovial hypertrophy score was able to differentiate clinically active from inactive JIA patients.

In this large cohort of JIA patients, findings from the physical examination did not correspond well with MRI-based disease activity scores. Even in patients who were considered to be moderately or severely active, synovial hypertrophy was present in only 61.9% and 83.3% of the patients, respectively. With respect to the minimal and moderate active JIA patients, synovial hypertrophy
was present in less than 50% of the children. Our results imply, therefore, that it is difficult to assess whether – for example – a joint is swollen due to inflammatory disease activity or due to other factors, such as subcutaneous fat or soft tissue edema (16). Furthermore, pain and limited range of motion in a joint are apparently not always an expression of inflammatory activity.

MRI has previously been shown to be more sensitive than the physical examination in the detection of active joint inflammation (2, 17). In the current study we confirm the high sensitivity of MRI in detecting subclinical synovitis, as synovial hypertrophy was still observed in 14 (35.9%) clinically inactive patients. Our results are in line with previous studies in JIA patients evaluating the presence of ongoing inflammation by ultrasound and MRI in clinically inactive JIA and RA patients (4, 6, 18-22). In RA patients, subclinical synovitis upon MRI proved to be associated with progressive radiographic damage (4). These results support the use of more complete contrast-enhanced MRI for accurate evaluation of the disease status in JIA patients. Once clinical measures have normalized, MRI may facilitate tailoring the therapeutic strategy, since physical examination by itself seems not be sufficient. On the other hand, the presence of subclinical synovial hypertrophy in JIA might be a remnant of active disease in the past, without relevant clinical consequences ('MRI-tis'). Whether this radiological feature of subclinical synovitis reflect a sign of ongoing inflammation and a potential flare of the disease should be formally addressed in prospective longitudinal outcome studies.

The lack of a significant correlation between the JAMRIS scores of inflammation with the patient's global assessment of overall well-being, the assessment of the patient's pain, and his functional ability is not surprising as these measures reflect – apart from disease activity – also damage done in the past (23). Furthermore, the lack of correlation with blood parameters of inflammation (ESR and CRP) is not unexpected, as these parameters indicate a systemic inflammation, while in this study the presence of MRI-detected disease activity in a single joint was sufficient to become included. On the other hand, the correlation between JAMRIS synovial hypertrophy scores and the physicians' global assessment of overall disease activity is promising, as this suggests that the knee as a major target joint might be representative of the overall burden of disease in JIA.

We used the JAMRIS system for standardised assessment of inflammatory and destructive changes in JIA. This method is easy-to-use, reliable and sensitive for evaluating disease status in JIA (15). With JAMRIS we were able to distinguish clinically active and inactive patients, indicating a good discriminative value. We now add another piece of evidence to support the applicability of the JAMRIS system as an outcome measure in daily practice and clinical trials in JIA.
A major limitation of our study is the lack of age-matched healthy controls. Since growing joints are subjected to change, it may be difficult to assess whether differences in the appearance of the knee joint are pathologic or form part of a child's normal development. For example, the prevalence of bony depressions and signal changes suggestive of bone marrow edema in wrists and knees of healthy children is high (24, 25). An MR imaging atlas of normal values regarding synovium, cartilage and bone in growing children is therefore warranted.

In summary, we can conclude that contrast-enhanced MRI is able to discriminate clinically active and clinically inactive JIA patients. Though, the physical examination is neither very sensitive nor specific in the evaluation of JIA disease activity. Subclinical synovitis can be detected in more than one third of the clinically inactive JIA patients. Physical examination should be supported by more sensitive tools such as MRI, in particular during monitoring treatment efficacy or while considering significant therapy changes.
References


