Magnetic resonance imaging in juvenile idiopathic arthritis diagnosis and follow-up, beyond imagination
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Chapter 10

Summary

Conclusions

Implications and future research
Summary

This thesis focuses on the development of MRI as an outcome measure in JIA. The feasibility, reliability, responsiveness, predictive value and discriminative value of MRI in the evaluation of disease status in JIA were evaluated. Furthermore we evaluated the value of the pixel-by-pixel DCE-MRI TIC-shape analysis method in discriminating clinically active and inactive JIA patients.

Although there is fair strength of evidence that MRI is an accurate diagnostic method for evaluating disease activity and for assessing clinical responsiveness to treatment in peripheral joints in JIA, there was no evidence supporting imaging of a specific joint within the scope of clinical trials. In chapter 2 the objective was therefore to assess 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. We analyzed patient charts of 95 JIA patients with a follow-up duration of at least 5 years. Our results showed that upon clinical assessment the knee is the most commonly affected joint in JIA both at the first visit (up to 77% of patients) and during a follow-up period of 5 years (up to 98% of JIA patients), 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.

In chapter 3 we determined the feasibility of bilateral non-contrast-enhanced open-bore MRI and evaluated the presence of literature based MRI features. For this purpose patients were classified in 2 clinical subgroups (e.g. active and inactive disease). An MRI protocol was developed for optimizing the feasibility of MRI in children by using an open-bore MRI system and omitting intravenous contrast-medium injection. MRI features were evaluated using a literature-based score. The complete MRI examination of both knees was successfully completed by all 47 children, the youngest being 5 years of age, indicating that this approach was promising. Synovial hypertrophy was more frequent in clinically active JIA patients (36.2%), but was also seen in 19.4% of the knees in JIA patients considered to be clinically inactive. Infrapatellar fat pad heterogeneity was more prevalent in chronic inactive JIA patients ($P = 0.008$). Reproducibility of the scored items was good (Cohen kappa, 0.49-0.96).

As the first literature based MRI score was broadly inclusive, in chapter 4 special attention was given to the refinement of this initial system in order to develop an easy-to-use scoring system. We assessed the reliability and responsiveness of a new Juvenile Arthritis MRI Scoring (JAMRIS) system.
for evaluating disease activity of the knee. For the purpose of this study MRI datasets of 25 JIA patients were independently scored by five readers using the JAMRIS system. JAMRIS comprises synovial hypertrophy, bone marrow changes, cartilage lesions and bone erosions. In addition, the JAMRIS system was determined as a follow-up parameter by two readers to evaluate response to therapy in 15 consecutive JIA patients. Our study showed good inter- (ICCs 0.86–0.95) and intra-observer (ICCs 0.92–1.00) reliability for the different items scored. Additionally, the scoring took an acceptable median of 6.6 minutes per patient, indicating good feasibility. Concerning therapy response, we observed a significant decrease in mean synovial hypertrophy scores (SRM -0.65).

Evidence lacked on the important practical issue of whether to use or not to use an intravenous injection of gadolinium-containing contrast agents in pediatric JIA patients. In chapter 5 we evaluated therefore the diagnostic accuracy and reliability of MRI without contrast enhancement in the evaluation of JIA knee joint abnormalities, compared with contrast-enhanced MRI as the reference standard. Imaging findings from 73 JIA patients were analyzed by two readers using the JAMRIS system. Our results showed that the agreement between contrast-enhanced and unenhanced MRI scores regarding bone marrow changes, cartilage lesions and bone erosions were good concerning sensitivity, specificity, negative predictive value, and positive predictive value. However, when contrast-enhanced MRI was considered the reference standard, unenhanced MRI scores were not as accurate (sensitivity 0.62) as contrast-enhanced MRI in the assessment of synovial hypertrophy.

To be valuable in daily practice and in clinical trials, an imaging measure should be able to discriminate patients or groups of patients in a most feasible, sensitive and reproducible way. As yet no studies had been performed to directly compare contrast-enhanced MRI and the physical examination in the assessment of JIA disease activity of the knee. In chapter 6 we evaluated the discriminative value of MRI in distinguishing active and inactive JIA patients and we assessed the diagnostic performance of MRI compared with the physical examination in the assessment of disease status in JIA patients. MRI datasets of 146 JIA patients were analyzed using the JAMRIS system. In this study, no differences were found between clinically inactive and clinically active JIA patients regarding MRI scores of bone marrow edema, cartilage lesions or bone erosions. Synovial hypertrophy scores differed significantly between both groups, indicating good discriminative value. On the other hand, synovial hypertrophy was also present in more than one-third of JIA patients with presumed clinically inactive disease. Regarding JIA patients considered to be clinically active, 48.6% showed no signs of MRI-based synovitis.
Before the value of MRI as an imaging bio-marker in daily practice, in research settings or clinical trials can be appropriately assessed, its sensitivity to detect clinical responsiveness to treatment over time will have to be determined. Therefore, in chapter 7 we assessed whether clinical disease activity findings during 1-year follow-up in JIA patients is associated with changes of MRI-based disease activity scores. Data of 40 patients with active knee involvement were analyzed. After follow-up of a median of 1.3 years, patients were re-evaluated and classified as “improved” or “not improved” according to the ACR Pediatric-50 criteria. Baseline and follow-up MRI features were scored by two readers using the JAMRIS system. After follow-up, 27 patients were classified as clinically improved, whereas 13 patients showed no clinical improvement. The clinically improved patients showed a significant reduction in synovial hypertrophy scores during follow-up (P < 0.001), with substantial effects (SRM -0.70). No such changes were observed for any of the other MRI features.

It is important to discriminate the different forms of arthritis in the early phase. A delay in treatment of JIA could lead to irreversible damage of the joint. In chapter 8 we evaluated whether clinical, laboratory or MRI measures were able to differentiate JIA patients from other forms of childhood arthritis in a patient group clinically suspected of non-infectious early (median 0.4 years) arthritis. For the purpose of this study, data of 80 consecutive treatment-naïve patients clinically suspected of JIA with active non-infectious arthritis of (at least) one knee for less than 12 months duration were collected. Upon presentation patients had clinical and laboratory assessments and contrast-enhanced MRI. Scoring radiologists were blinded for laboratory findings and clinical activity. Of the patients, 44 out of 80 were diagnosed on clinical ground with JIA and categorized according to the ILAR criteria, whereas in 36 patients the diagnosis of JIA was discarded based on clinical or laboratory findings. Our results showed that 5 factors (male gender, physician’s global assessment of overall disease activity, number of joints with limited range of motion, HLA-B27, MRI-based synovitis) were associated with the onset of JIA. In multivariate analysis only MRI-based synovitis proved to be independently associated with JIA (OR 6.58, 95% CI 2.36-18.33).

MRI lacks quantitative analysis methods for the assessment of disease activity and for monitoring the individual patient response to therapy. In both JIA and adult rheumatoid arthritis, dynamic DCE-MRI has been suggested as an accurate and objective outcome measure. In chapter 9 the aim of our study was to assess the discriminative value of the DCE-MRI pixel-by-pixel analysis method by comparing semi-quantitative descriptive DCE-MRI parameters and the relative number of TIC shapes as derived from DCE-MRI between knees of clinically active and clinically inactive JIA patients. JIA patients were classified into two clinical groups: active disease and inactive disease.
Statistical DCE-MRI measures of each voxel were calculated in a three-dimensional volume of interest of the synovial membrane. Significantly higher numbers of TIC shape 4 ($P = 0.001$), median ME ($P = 0.004$), MIS ($P = 0.001$), iAUC ($P = 0.002$), and EV ($P = 0.013$) were observed in clinically active compared with inactive patients. TIC shape 5 was more present in the clinically inactive patients ($P = 0.018$).
Conclusions

Chapter 2. The knee is upon clinical assessment the most commonly involved joint at onset and during follow-up in JIA, followed by the ankle, elbow and wrist. The knee can, therefore, be considered as the most appropriate joint to be used as outcome for MRI.

Chapter 3. Bilateral non-contrast-enhanced open-bore knee MRI is feasible in the assessment of disease activity in unsedated children with JIA. Signs differing among children with active and inactive disease include infrapatellar fat pad heterogeneity and synovial hypertrophy. Our study indicated that creating an MRI scoring system for knee joint pathologies in JIA is possible, with moderate to good reproducibility.

Chapter 4. The JAMRIS system proved to be a simple and highly reliable assessment score in the evaluation of JIA disease activity of the knee. The use of JAMRIS as a follow-up parameter for synovial hypertrophy is promising.

Chapter 5. Unenhanced MRI enables reliable assessment of bone marrow changes, cartilage lesions and bone erosions as joint abnormalities in knees of patients with proven JIA. However, omission of intravenous contrast leads to an increase in inter-reader variation and decreases the sensitivity for scores of synovial hypertrophy. Omitting intravenous Gd in the MRI assessment of joints in JIA is therefore inadvisable.

Chapter 6. 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. Physical examination should be supported by more sensitive tools such as MRI, in particular during monitoring treatment efficacy or while considering significant therapy changes.

Chapter 7. There is a strong association with clinical improvement according to the ACR Pediatric-50 criteria and changes in MRI-based synovial hypertrophy scores, supporting the role of MRI as a responsive outcome measure to evaluate disease activity in response to anti-inflammatory treatment strategies.
Chapter 8. The presence of MRI-based synovitis is significantly associated with the clinical onset of JIA. Physical examination could be supported by MRI, particularly to contribute in the early differentiation of different forms of non-infectious childhood arthritis.

Chapter 9. The pixel-by-pixel DCE-MRI TIC-shape analysis method proved capable of differentiating clinically active from inactive JIA patients by the difference in the number of TIC shapes 4 and 5, as well as by the descriptive parameters ME, MIS, iAUC and EV.
Implications and future research

Conventional imaging has played an important role in the management of JIA. The trend towards early suppression of inflammation in order to prevent irreversible damage of cartilage and bone shifts the emphasis from conventional radiography detectable damage to early stage manifestations of JIA. This drives the need for imaging techniques that are more sensitive in the evaluation of inflammatory processes as well as early erosive changes. In this regard MRI and ultrasonography have been playing an increasing role in evaluating and monitoring of disease in JIA patients. The development of an MRI outcome measure for the assessment of disease status in JIA is important. The increasing evidence that early therapeutic intervention improves long-term outcome and the development of very effective treatments highlights the need for objective and accurate measures in the assessment of disease activity, individual response to therapy, efficacy of treatment and long-term outcomes in JIA (1-3). Presently, the physical examination remains the gold standard for identification of disease activity in both daily practice and clinical trials. However, it has, even by an experienced observer, only limited reliability (4). Moreover, advances in therapies have increased the number of patients who reach clinically inactive disease, but this cannot always be reliably demonstrated by physical examination alone (5-9). Despite the large number of studies available in adults, 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 daily practice and clinical trials relates to the lack of standardization of protocols and scales for data acquisition and interpretation, respectively. We focused on this piece of missing evidence in the literature. Therefore, we developed and validated an easy-to-use and highly reliable scoring method (JAMRIS) for the standardized evaluation of disease status of the knee, as the most commonly affected joint in JIA. The work described in this thesis demonstrates that contrast-enhanced MRI with the use of JAMRIS for the knee has great potential to serve as an outcome measure in daily practice and clinical trials in JIA. It is a feasible, reliable and responsive technique in children with JIA as young as 5 years of age. However some important limitations regarding the use of MRI should first be resolved.

The use of the JAMRIS system as an outcome measure in daily practice and clinical trials is promising. Thus far, JARMIS has only been tested in JIA patients visiting referral pediatric rheumatology centers in the Netherlands with full access to current treatment (AMC and Reade). This has resulted in a population of studied JIA patients with only mild-to-moderate disease
activity. Consequently, the presence of destructive changes of cartilage and bone was relatively low. To evaluate the value of JAMRIS as a sensitive measure regarding these destructive changes, additional research is necessary. For further validation of the JAMRIS system (inter)national collaboration is warranted, especially with research centers with access to more severely affected JIA patients. Interaction between researchers and health professionals in the field of imaging in JIA is essential to obtain international consensus and continuous improvement of MRI outcome measures. Such collaboration will be expected to be very fruitful under the umbrella of an international, well-accepted collaborative international group such as the Outcome Measures in Rheumatology (OMERACT) working group.

Aging joints are subjected to change. Therefore it is difficult to establish whether differences in the appearance of the knee joint upon MRI are pathologic or form part of normal maturation. For example, the prevalence of bony depressions and signal changes suggestive of bone marrow edema in wrists and knees of healthy children is high (10, 11). Currently, it lacks imaging atlases of normal measurements in growing joints. Without expert discussion on how to solve the challenges in interpretation of MRI of growing joints, the development of appropriate MRI scales to measure changes in growing joints will be seriously impacted. This will ultimately affect health care of JIA. Therefore, in order to effectively evaluate the efficacy of treatment in clinical trials and other research, we need to create imaging atlases to differentiate physiologic and pathologic joint findings in children and teenagers with JIA.

The use of MRI as an imaging bio-marker in clinical practice is restricted due to some practical limitations. For instance, the cost-effectiveness of MRI in the evaluation of disease status in JIA has never been evaluated. Secondly, there is no consensus on which joints should be used for disease assessment and monitoring response to therapy. Moreover, there are some considerations of the feasibility and appropriate training required to use MRI in clinical practice. Altogether, there is still a large amount of research mandatory to optimize the use of MRI in clinical practice.

As a collaborative group, OMERACT was created to improve outcome measures in rheumatology through a data driven interactive consensus process. In adult rheumatology, members from different countries and international opinion leaders have developed guidelines and recommendations on outcome measures. Recently, a special interest group (SIG) on imaging outcome measures in pediatric rheumatic diseases has been established, with a leading role for researchers and clinicians based at the AMC. This international cooperation is extremely important to develop consensus guidelines for imaging outcomes in JIA. Our OMERACT SIG on MRI in JIA has brought together
leading experts in rheumatology and imaging. This SIG will build on the experience and know-
how of the research team and the work conducted by the existing OMERACT group. Although
the first few steps towards the development of evidence based guidelines for MRI data acquisition
and interpretation has been made, further cooperation is necessary. Further collaboration should
focus on the development of an MRI atlas of healthy joints in children, obtaining agreement on
an optimal imaging protocol for knee, wrist and TMJ, and further development and validation of
scoring methods for MRI of the knee, wrist and TMJ.

Another point of discussion is the lack of knowledge on the significance of MRI in the assessment
of subclinical synovitis. Some important questions can be raised when such data would come
available over time. First, does this radiological feature of subclinical synovitis reflect a sign of
ongoing inflammation and potential flare of the disease or progressive joint damage over time,
when medical treatment will be stopped for clinical reason of remission of disease? Secondly,
does the radiological mark of subclinical synovitis reflect a symptom that may become leading
in our decision-making regarding stop-rules and/or continuation of treatment in JIA? The value
and meaning of subclinical synovitis has, therefore, to be determined in prospective follow-up
studies. Another discussion raised by sensitive imaging results may be directed at the value of
the clinical categorization into mono-articular, oligo-articular and/or poly-articular disease. To date,
the categorization is based on clinical scores instead of imaging and it remains to be clarified
whether this is sufficient in understanding the pathophysiology of the disease, or in prediction of
outcome or treatment response. Changes in categorization can have great consequences when
treatment decisions are based on the JIA category.

To date, MRI is the state-of-the-art imaging technique able to visualize bone marrow changes
suggestive for bone marrow edema. Longitudinal studies have shown that the presence of bone
marrow edema is a key predictor of early erosive joint damage in adults with rheumatoid arthritis
(12, 13). However, no longitudinal studies assessing the prognostic value of bone marrow edema
in the development of destructive changes in JIA patients have been performed. It is, therefore,
possible that the presence of bone marrow edema is an over-estimated imaging feature, as
these bone marrow changes might be characteristic of normal development and maturation in
children. Therefore, an MRI dataset of healthy children should be created and evaluated for the
presence of bone marrow changes suggestive of bone marrow edema. Moreover, the value of
bone marrow edema in predicting erosive changes in children with JIA has to be determined in
longitudinal follow-up studies.
Another interesting point is the use of advanced MRI techniques for the evaluation of inflammatory and destructive changes in JIA, including DCE-MRI, T2-mapping and diffusion-weighted imaging (DWI). Currently, advanced imaging techniques are used particularly in the context of research and to a lesser extent in daily practice. Moreover, correlation with clinical parameters is still lacking. The exact value of advanced MRI techniques in JIA patients have to be determined in larger prospective studies. To be viable in daily practice, these imaging-techniques should be sensitive to change on which no evidence is available yet. The further development and implementation of advanced imaging techniques in research is important. Especially the contrast-free approach of – for example – DWI is highly desirable in clinical practice, because it will substantially improve patient care by optimizing feasibility of MRI in pediatric JIA patients.

The development of state-of-the-art MRI techniques for JIA evaluation, combined with the necessity for better monitoring of disease and treatment efficacy highlight the need for further validation of these advanced imaging techniques. One of the most powerful features of MRI consists of the DCE-MRI technique to quantitatively measure the dynamic characteristics of the tissue, such as vascularization, tissue perfusion, and capillary permeability. Further validation of the pixel-by-pixel DCE-MRI TIC-shape analysis method is necessary to determine its potential role in evaluating disease activity and response to therapy in JIA. In this thesis, the discriminative value and feasibility of DCE-MRI was evaluated. However, essential information on its responsiveness and predictive value is still lacking. Furthermore the possibility to combine the TIC shape with the other semi-quantitative measures (ME, etc) to provide a multi-feature analysis should be further investigated. Moreover, the additional value of DCE-MRI compared to conventional MRI measures (JAMRIS) has to be determined.

In this thesis we tried to answer a number of relevant clinical questions. Partially, we succeeded. However, in science one answer raises more questions. Therefore, the most important topics for future research are shown in Table 1.
Table 1. Future research agenda

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