Selecting Magnetic Resonance Imaging (MRI) Outcome Measures for Juvenile Idiopathic Arthritis (JIA) Clinical Trials: First Report of the MRI in JIA Special Interest Group

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ABSTRACT. Recent advances in magnetic resonance imaging (MRI) techniques have substantially improved the evaluation of joint pathologies in juvenile idiopathic arthritis (JIA). Because of the current availability of highly effective antirheumatic therapies and the unique and useful features of MRI, there is a growing need for an accurate and reproducible MRI assessment scoring system for JIA, such as the rheumatoid arthritis MRI Scoring (RAMRIS) for patients with rheumatoid arthritis (RA). To effectively evaluate the efficacy of treatment in clinical research trials, we need to develop and validate scoring methods to accurately measure joint outcomes, standardize imaging protocols for data acquisition and interpretation, and create imaging atlases to differentiate physiologic and pathologic joint findings in childhood and adolescence. Such a standardized, validated, JIA-MRI scoring method could be used as an outcome measure in clinical trials. (First Release Nov 1 2013; J Rheumatol 2014;41:354–8; doi:10.3899/jrheum.131081)

Key Indexing Terms: MAGNETIC RESONANCE IMAGING CHILDREN JUVENILE IDIOPATHIC ARTHRITIS GUIDELINES SCORING SYSTEMS

Prior to the Outcome Measures in Rheumatology (OMERACT) 11 meeting, a special interest group (SIG) on magnetic resonance imaging (MRI) in juvenile idiopathic arthritis (JIA) was formed to prepare content for the SIG meeting. During the SIG meeting, a summary of previous work conducted by the group investigators was presented:

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(1) results of a retrospective study on the frequency of joint involvement in JIA (unpublished data); (2) results of 2 online questionnaires; and (3) an overview of the current literature regarding available MRI scoring methods in JIA. Participants agreed that development of MRI guidelines and outcome measures in JIA is important, with significant scientific and clinical implications. This SIG will concentrate efforts on the development and further refinement of standardized MRI scoring systems. Following presentation of results from data obtained a priori and discussion of points raised by participants, we concluded that the SIG would focus on the development of MRI scales at 3 joint levels: (1) large joints (knees and ankles), (2) small joints (wrists and hands), and (3) temporomandibular joints (TMJ). The rationale for our approach was that the methodological concept for inclusion of items in MRI scales that assess different types of joints is distinct. Therefore, the short-term focus of our group will be the joint-based 3-pillar development of MRI scoring systems.

JIA is the most common autoinflammatory musculoskeletal disease in childhood, with a yearly incidence in developed countries of 2–20 cases/100,000 and a prevalence that varies between 16 and 150 cases/100,0001. JIA is not a solitary entity, but a term that encompasses all forms of arthritis that begin before the age of 16 years, persist more than 6 weeks, and are of unknown etiology and pathophysiology2. The clinical presentation of JIA is characterized by joints with swelling and tenderness or pain on motion and

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The radiological evaluation of children’s joints is challenging. Skeletal growth and maturation in children are dynamic processes, and therefore may make it difficult to establish whether differences in the appearance of growing joints are pathologic or part of normal skeletal maturation. Currently, conventional radiography (CR) is the most commonly used imaging modality for evaluation of structural damage in JIA. It is the traditional standard for assessment of growth abnormalities or joint damage, including bone erosions, joint space narrowing, joint subluxation, malalignment, and ankylosis. With the recent development of highly effective therapies, the main goal of treatment has become the total suppression of joint inflammation to prevent destructive changes; therefore, outcome measures in clinical trials should comprise sensitive and reliable measures of inflammation. Although CR provides important information with respect to growth abnormalities and damage due to persistent disease activity in JIA, early changes may not be found with this imaging modality, and late changes can be permanent. For example, some early erosive changes can easily be detected by MRI, but are unidentifiable by CR. In addition to these findings it is important to note that it remains challenging to establish whether these MRI features are pathologic or part of the normal maturation process. Although CR remains the reference standard for imaging long-term outcome of bony structures, it is unsuitable for imaging another structural hallmark of JIA joint disease, i.e., the presence of synovial hypertrophy. The trend toward early suppression of inflammation to prevent cartilage lesions and bone erosions has shifted emphasis from CR-detectable damage to early stage manifestations of JIA, which drives the need for imaging techniques that are more sensitive in the evaluation of inflammatory processes and early erosive changes. In this regard, MRI and ultrasonography are playing bigger roles in evaluating disease status and following up patients with JIA.

MRI is the preferred imaging modality for detection of synovial inflammation, early destructive changes, and bone marrow changes in JIA. MRI using an intravenous contrast agent provides better differentiation between joint effusion and synovial hypertrophy through better visualization of hypervascularity of the inflamed synovial membrane, reflecting ongoing inflammation. Despite the large number of studies available in adults, experience in the use of MRI in the assessment of JIA is limited. Hence, this technique is underused in both clinical practice and research. Part of the reason for the underuse of MRI as an outcome measure in clinical trials of JIA is the lack of standardized protocols and scales for data acquisition and interpretation, respectively, in the literature. In addition, because thinning of articular cartilage can be either physiologic or pathologic, early destructive changes in joints of young children may be masked on MRI because of greater thickness of epiphyseal cartilage in these joints, which makes evaluation less accurate. To our knowledge, very few MRI scales have been designed to specifically assess morphologic changes in growing joints. At this point no imaging atlas of normal measurements in growing joints is available in the literature. 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 limited, ultimately affecting the care of patients with JIA. Therefore, to properly evaluate the efficacy of treatment in clinical trials and other research, we need to develop and validate scoring methods to accurately measure joint outcomes, standardize imaging protocols for data acquisition and interpretation, and create imaging atlases to differentiate physiologic and pathologic joint findings in childhood and adolescence. Subsequently, this standardized, generally accepted JIA-MRI scoring method can be used as an outcome measure in clinical trials.

Proceedings
Prior to the OMERACT 11 meeting, a SIG on MRI in JIA was formed to prepare content for the SIG meeting. Included in the working group were a pediatric rheumatologist (MvR), a pediatric radiologist (AD), a research fellow (RH), and a SIG mentor (DvdH). The SIG comprised 34 interested experts in the field of imaging in JIA: 19 (pediatric) rheumatologists and 15 (pediatric) radiologists from 10 different countries.

Presentation of Data
The SIG meeting began with a short presentation, starting with the rationale for further development and refinement of MRI as an outcome measure in JIA for use in future clinical
research trials. Next, results of a study on the frequency of joint involvement in JIA and the results of 2 online questionnaires were discussed. Thereafter, an overview of the current literature regarding available scoring methods was provided, followed by a presentation on the value of MRI in the assessment of disease status of the TMJ in JIA and the need for an objective outcome measure for this particular joint.

Frequency of joint involvement in JIA. Before recommendations can be made with respect to imaging protocols for data acquisition on children and adolescents with rheumatologic diseases, the most appropriate joint(s) to be used as outcome for research have to be selected. One of the objectives prior to the OMERACT 11 meeting was to assess the sequence and type of active joints in a cohort of newly diagnosed patients with JIA at first visit and during a followup period of 5 years, to identify an index joint/group of joints for MRI in JIA. During the SIG meeting we discussed results of the retrospective study, in which data of newly diagnosed JIA patients with consistent followup duration of at least 5 years were analyzed. Moreover, we concluded that from disease onset the knee is the most commonly affected joint in JIA, followed by the ankle, elbow, and wrist (unpublished data).

Online questionnaires. Two online questionnaires were sent to the 34 interested experts. Questionnaire 1 focused on expert opinion regarding target joints for MRI in clinical trials. The questionnaire included 9 questions regarding joints to be included in the imaging protocol of clinical trials. Additionally, the survey evaluated which joints experts wanted to start with in development of standardized assessment procedures. Results of the questionnaire showed that the knee, wrist, and TMJ were considered to be the most appropriate target joints for MRI in clinical trials.

Questionnaire 2 focused on expert opinion regarding MRI features to be included in an MRI scoring system assessing JIA. In addition, it was evaluated which bones and joints of the hand and wrist should be included in standardized assessment procedures. Moreover, expert opinion was obtained on the use of intravenous contrast enhancement and on the acceptable duration of an MRI protocol. Results of the questionnaire showed that the distal radius and ulna as well as proximal joints (carpal, base of metacarpals) were considered to be most relevant for scoring purposes, and that contrast-enhanced MRI was essential for the evaluation of JIA. Experts indicated that the imaging protocol should not take longer than 30 min.

Available scoring methods for MRI in JIA. Later during the meeting, available MRI scoring methods for evaluation of disease status in JIA were presented. Two scoring systems were presented, 1 focusing on the wrist33 and 1 focusing on the knee35. Both scoring systems evaluate inflammatory and destructive changes.

The first scoring system, published by Malattia, et al33, evaluates 3 MRI features: synovial hypertrophy (0–3), bone marrow edema (0–2), and bone erosions (0–4). Definitions of scored items, anatomical regions, and grading were adapted from the RAMRIS system36. The second scoring method, the Juvenile Arthritis MRI Scoring (JAMRIS) system for the knee35, evaluates 4 features including synovial hypertrophy, bone marrow edema, cartilage lesions, and bone erosions. Synovial hypertrophy (0–2) is evaluated at 6 sites of the knee joint, and scored based on the maximal thickness in any slice at each site. For scoring bone marrow edema (0–3), cartilage lesions (0–3), and bone erosions (0–3), the knee is divided into 8 anatomical regions. Definitions of scored items, anatomical regions, and grading were adapted from studies performed by Østergaard, et al36, Guermazi, et al37, and Gylys-Morin, et al25,26. The 2 proposed scoring methods proved to be reliable and sensitive to change in studies by the developers. However, no validation studies by different groups or observers have been published.

Presentation on the TMJ in JIA. A presentation was given on the value of MRI for early diagnosis of TMJ involvement in JIA38,39. The clinical relevance of early detection of TMJ involvement is great because its destruction can cause severe craniofacial growth disturbances. Because of a lack of standardized and validated scoring methods for the assessment of TMJ disease status, it was discussed that there is a need for standardized MRI outcome measures for this joint.

Discrepancy in Survey Results

Although the retrospective study showed that the knee is the most commonly affected joint in JIA (followed by the ankle, elbow, and wrist), it was discussed that the TMJ is often involved but missed in the clinical examination. TMJ appears to require specific attention owing to its vulnerability in the presence of persistent inflammation. Results of the online questionnaires showed that most experts think the wrist (followed by the knee) should be the target joint for clinical trials and development of MRI scales for JIA.

Conclusions. Based on results of the retrospective studies and the online questionnaire, we concluded that joints of greatest interest are the knee, wrist, and TMJ. Further, we concluded that MRI features of greatest interest are synovial hypertrophy, bone marrow edema, cartilage lesions, and bone erosions.

Discussions with Participants

Based on discussions during the SIG meeting, a procedure for development of an MRI scale was suggested, beginning with the knee, wrist, and TMJ. Participants agreed that the development of MRI guidelines and outcome measures in JIA was important, with considerable scientific and clinical implications. The SIG should continue its work to develop and refine standardized MRI scoring systems.

It was also discussed that there are no validated and
widely used scoring systems available for the standardized evaluation of ultrasonography or CR in JIA, which makes comparison between different imaging modalities challenging. Another point raised was a lack of information regarding construct validity of the discussed MRI scores. Therefore, information about how MRI correlates with physical examination should be obtained. Further, the lack of literature regarding normal MRI measurements of joint fluid, synovium, and cartilage in healthy children and adolescents of different age groups is a potential limitation for the development of MRI outcome measures in pediatric patients with JIA. Because joints are maturing, it may be difficult to establish whether differences in the appearance of the joint are pathologic or part of normal maturation. Given the lack of data on the normal appearance of pediatric joints, it was suggested to use contralateral unaffected joints as “control joints” in future clinical trials of unilateral arthritis whenever possible.

Research Agenda
- Develop an MRI atlas of healthy joints at different ages
- Obtain agreement on an optimal imaging protocol for knee, wrist, and TMJ
- Develop and validate scoring methods for MRI of the knee, wrist, and TMJ
- Acquire data on the performance of MRI in assessing anatomical joint status in JIA
- Obtain information on the correlation between MRI and clinical characteristics of disease status in JIA (truth)

Based on results of questionnaires and a retrospective study performed prior to the OMERACT 11 meeting, we concluded that SIG on MRI in JIA should focus on development of 3 MRI scales: (1) large joints (knees and ankles), (2) small joints (wrists and hands), and (3) TMJ. This strategy is based on the methodological concept for inclusion of items, which is distinct for developing MRI scales for large joints, small joints, and TMJ, although primarily synovial hypertrophy, bone marrow edema, cartilage lesions, and bone erosions are features of the highest interest.

REFERENCES


Papers presented at the OMERACT 11 Conference,
Pinehurst, NC, USA, May 12–17, 2012

Part 1 Methods

Part 2 Imaging and Other Biomarkers

Part 3 Disease Specific Outcomes I

Part 4 Disease Specific Outcomes II

Part 5 The OMERACT Filter 2.0

Part 3 will appear in the March issue.