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Research article

Normal MRI findings of the knee in patients with clinically active juvenile idiopathic arthritis

E. Charlotte van Gulik[a,b,*], Robert Hemke[a], Mendy M. Welsink-Karssies[b], Dieneke Schonenberg-Meinema[b], Koert M. Dolman[c,d,e], Anouk M. Barendregt[a,b], Charlotte M. Nusman[a,b], Mario Maas[a], Taco W. Kuijpers[b], J. Merlijn van den Berg[b]

[a] Department of Radiology and Nuclear Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105AZ, Amsterdam, The Netherlands
[b] Department of Pediatric Hematology, Immunology, Rheumatology and Infectious Diseases, Emma Children's Hospital AMC, University of Amsterdam, Meibergdreef 9, 1105AZ, Amsterdam, The Netherlands
[c] Department of Pediatric Rheumatology, Reade, Dr. Jan van Breemenstraat 2, 1056AB, Amsterdam, The Netherlands
[d] Department of Pediatric Rheumatology, OLVG West, Jan Tooropstraat 164, 1061AE, Amsterdam, The Netherlands
[e] Department of Pediatric Rheumatology, OLVG Oost, Oosterpark 9, 1091 AC, Amsterdam, The Netherlands

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ABSTRACT

Objective: In a number of patients with clinically active juvenile idiopathic arthritis (JIA), contrast-enhanced MRI shows no signs of synovitis. The objective of this study was to assess the frequency and the patient characteristics in clinically active JIA patients in which MRI showed no signs of synovitis.

Methods: From our cohort of 313 patients in which contrast-enhanced MRI of the knee had been performed, we selected 72 JIA patients with clinically active disease involving the target joint. The validated Juvenile Arthritis MRI Scoring (JAMRIS) system was used to evaluate synovial thickening. Patients were divided into two groups based on MRI outcome: Group 1: thickened synovium on MRI (JAMRIS score ≥1) or Group 2: normal synovium on MRI (JAMRIS score 0). Patient characteristics and disease activity parameters were then compared.

Results: In 35% (25/72) of these patients, MRI results contrasted with the clinical assessment (Group 2). In comparison to Group 1, the patients with discrepant findings were significantly older at the date of examination and JIA had been diagnosed at later age (median age of 13.2 vs. 10.9 and median age 10.0 vs. 8.0 respectively). In Group 2 there were significantly more patients with RF-negative polyarticular disease.

Conclusion: Patients with RF-negative polyarticular JIA who had been diagnosed at a later age and were older at the time of MRI were most likely to be considered clinically active while MRI showed no signs of synovitis. These particular JIA patients may benefit from monitoring of disease activity by MRI to prevent overtreatment.

1. Introduction

Juvenile idiopathic arthritis (JIA) represents a heterogeneous disease defined by arthritis in one or more joints with an onset before the age of sixteen, lasting more than six weeks and without an evident cause [1]. The hallmark of JIA is auto-immune synovitis and therapy is based on suppressing this inflammation. At physical examination, it can be difficult to accurately assess the presence or absence of synovitis in a joint, which complicates treatment decisions. Presumably, this leads to overtreatment in some patients and undertreatment in others, which might result in unnecessary exposure to side-effects or irreversible joint destruction respectively.

Several scoring systems have been developed to aid clinicians in deciding whether to start, continue or stop treatment in individual patients, such as the Juvenile Arthritis Disease Activity Score (JADAS) [2] and the disease activity levels according to the American College of Rheumatology (ACR) [3,4]. Parameters on which these systems are developed are: physical examination, laboratory measurements such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) and patient reported outcome measures (PROMs). However, all these parameters have limitations, which hamper optimization of a "personalized medicine" strategy.

* Corresponding author at: Academic Medical Center, University of Amsterdam, Department of Radiology and Nuclear Medicine (G1-226), Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands.
E-mail addresses: e.c.vangulik@amc.uva.nl (E.C. van Gulik), r.hemke@amc.uva.nl (R. Hemke), m.m.karssies@amc.uva.nl (M.M. Welsink-Karssies), d.schonenberg@amc.uva.nl (D. Schonenberg-Meinema), k.dolman@reade.nl (K.M. Dolman), a.m.barendregt@amc.uva.nl (A.M. Barendregt), c.m.nusman@amc.uva.nl (C.M. Nusman), m.maas@amc.uva.nl (M. Maas), t.w.kuijpers@amc.uva.nl (T.W. Kuijpers), j.m.vandenberg@amc.uva.nl (J.M. van den Berg).

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When the physical examination and above-mentioned parameters do not provide the clinician with a clear-cut answer, magnetic resonance imaging (MRI) is increasingly being used for further decision making in JIA. MRI seems to be more specific than clinical assessment in showing signs indicative of synovitis. However, appreciation of these findings is difficult because of discrepancies between the clinical assessment and MRI findings are described in up to 50% of the cases [5–7]. Histology is considered to be the gold standard. In a comprehensive review, McQueen pointed out the high correlation between the rate of synovial enhancement on MRI and histological examination in determining synovitis in rheumatoid arthritis (RA) [8]. The correlation between MRI and histology in JIA is unknown since biopsies are rarely performed.

Different hypotheses exist on synovial thickening on MRI in clinically inactive patients; synovial thickening on MRI is either seen as subclinical disease warranting treatment or as a remnant of previous inflammation without clinical significance [9–12].

On the other hand, the sensitivity of MRI in showing synovitis is considered much higher compared to physical examination, ultrasound or conventional radiography. Therefore, treatment decisions can be made in the *absence* of inflammatory signs on MRI even though the patient is considered to be clinically active. We hypothesized that a thorough analysis of clinical data and MRI findings in patients with clinically active JIA without signs of synovitis on MRI could further substantiate the significance of the MRI findings. Consequently, it might be possible to differentiate subgroups of JIA patients who could benefit from MRI prior to treatment decisions.

2. Material and methods

This study was conducted in compliance with the Helsinki Agreement. The requirement for informed consent was waived by the local ethical committee, since the data used for this study consists of data which is collected in the standard clinical setting and is stored according to Good Clinical Practice (GCP) guidelines.

2.1. Patient selection

Since 2008, data of patients with JIA and data of patients suspected for JIA who underwent an MRI in our centre have been prospectively collected. Data of these patients are stored in our JIA database.

All patients involved in this study (December 2008 to October 2014) underwent clinical and laboratory assessment, followed by contrast-enhanced MRI of the knee based on a clinical indication. Indications include baseline MRI before (altering) treatment, detection of structural joint damage or detection of persisting arthritis while on medication. Treatments were not changed prior to imaging.

This study focused on the knee, being the most commonly involved joint in JIA [13]. Inclusion criteria were: (1) patients fulfilling the ILAR criteria for JIA, defined as arthritis of unknown etiology that begins before the age of 16 and persists for at least 6 weeks [14] and (2) clinically evident knee arthritis, defined as the presence of swelling within the joint or limitation of motion combined with tenderness or pain of the joint [14]. Patients were excluded if (1) the MRI was not performed within three months after the clinical assessment, (2) if Wallace criteria for inactive disease were fulfilled [4], defined as having no joints with active arthritis; no fever, rash, serositis, splenomegaly or generalized lymphadenopathy attributable to JIA; no active uveitis; ESR or CRP level within normal limits and a best possible score for the physician's global assessment of disease activity on the scale used, (3) if the paediatric rheumatologist was in doubt regarding clinical assessment, (4) if the patient underwent a steroid injection in the target joint within 6 months prior to MRI. When more joints were considered to be clinically affected, the most severely affected joint of a JIA patient was subject for evaluation with MRI to serve as an accurate representation of the disease activity of all joints.

2.2. Clinical assessment

The clinical assessment was performed by one of our experienced paediatric rheumatologists, ranging from 3 to 20 years of experience. An 84-joint count defining presence of swelling, pain, limited range of motion and warmth was registered. Additionally, disease activity was scored using a five-point Likert scale. The disease status was noted i.e. treatment-naive, defined as never before received treatment with a disease-modifying antirheumatic drug (DMARD), or relapse/smouldering. A visual analogue scale (VAS) (range 0–100 mm, with 0 being the best score) was used to semi-quantify the physicians' global assessment of disease activity, patient's global assessment of well-being and patient's assessment of pain. Consequently, the Juvenile Arthritis Disease Activity Score (JADAS-10) was calculated [2]. Functional ability was measured with the use of the Dutch version of the childhood health assessment questionnaire (CHAQ) [15]. Medication use was registered. General and immunological laboratory tests included ESR, CRP, IgM RF, ANA, HLA-B27 and anti-CCP.

2.3. MRI protocol

An open-bore 1.0T MRI scanner with a dedicated knee coil (Panorama HFO, Philips Medical Systems, Best, The Netherlands) was used to perform MRI of the target knee. Patients were situated in supine position with the knee centrally in the magnetic field. MRI sequences included the following: T2-weighted SPIR with fat-saturation in sagittal, coronal, and axial plane (repetition time (TR) 2700–4500 ms, echo time (TE) 50 ms, matrix 300 × 270); sagittal T1-weighted turbo spin echo, fat-suppressed images (TR 515–591 ms, TE 10 ms, matrix 332 × 236); and after IV contrast injection, an axial T1-weighted fat-saturated SPIR sequence (TR 588–591 ms, TE 10 ms, matrix 272 × 192) and an sagittal T1 turbo spin echo sequence (TR 518–592 ms TE 10 ms matrix 332-236) were obtained. Slice thickness for all sequences was 4 mm and the field of view 150 × 150 mm. The post-contrast images were obtained within ten minutes after IV injection of a gadolinium-containing contrast agent (0.1 mmol/kg of body weight, gadobutrol; Bayer Healthcare, Berlin, Germany).

2.4. Image analysis

The MRI dataset was scored by one reader (6 years of experience in musculoskeletal radiology) who was blinded to the clinical disease state of the patients. In order to quantify disease activity on MRI, synovitis was scored using the validated, synovial hypertrophy score of the Juvenile Arthritis MRI Scoring system (JAMRIS) [16]. In the JAMRIS, synovitis is defined as an area of increased signal of the synovial compartment on MRI that shows a thickness greater than the width of the normal synovium (normal < 2 mm). The synovium is scored at 6 different locations in the knee joint. Per location a score of 0, 1 and 2 can be given, resulting in a maximum score of 12 [16]. A JAMRIS hypertrophy score of ≥1 is considered positive and interpreted as synovitis.

2.5. Statistical analysis

Descriptive statistics of patient characteristics and disease activity parameters were reported. Since data were not normally distributed, non-parametric tests were used to test for differences between patients with and without signs of synovitis on MRI. The Fisher's exact test was used to analyse differences between groups if data were categorical (gender, ILAR category, ANA, HLA-B27). The Mann–Whitney *U* test was used to analyse differences between groups if data were continuous (age, disease duration, number of active joints, CHAQ, JADAS-10, VAS, ESR, CRP). All tests assumed a two-tailed probability and a p-value of < 0.05 was considered as a significant difference. No correction for multiple testing was applied due to the exploratory nature of this study