Magnetic Resonance Imaging Identifies Features in Clinically Unaffected Knees Predicting Extension of Arthritis in Children with Monoarthritis

JANET M. GARDNER-MEDWIN, ORLA G. KILLEEN, CLIVE A J. RYDER, KAREN BRADSHAW, and KARL JOHNSON

ABSTRACT. ***Objective.*** A proportion of children with oligoarthritis have an aggressive disease course. Identifying these children at presentation would help guide prognosis and management. We examined if magnetic resonance imaging (MRI) of clinically unaffected joints is more sensitive than clinical assessment in identifying those at risk of developing arthritis in more than one joint.

Methods. Ten children were recruited; they had a mean age of 9.4 (range 5.2–14.2) years at presentation of a monoarthritis. MRI of a clinically unaffected knee was performed within 4 months of presentation, and was reported by 2 pediatric radiologists blinded to the clinical findings. All MR examinations included post-gadolinium sequences. Joints with clinically apparent arthritis were recorded regularly over a median of 37.0 (range 6.6–47.0) months by a median of 6.0 (range 2–8) pediatric rheumatologists blinded to the MR result.

Results. Four children developed arthritis in other joints over a median of 3.9 (range 3–6) months after the MRI scan; all had abnormal MRI scans at presentation. Three of these developed clinical features in the previously normal knee 4–11 months after MRI identified small joint effusions, synovial hypertrophy, and lymph node enhancement. One child developed a polyarthritis, but never developed clinical features in the imaged knee over 3.8 years of followup. Four other children had a persistent monoarthropathy with a median followup of 29.5 (range 6.6–42.0) months. All 4 had normal MRI. Two children had reactive arthritis.

Conclusion. MRI distinguished between patients with a persistent monoarthritis and those who developed further clinical arthritis up to 1 year later. The results suggest a widespread inflammatory process may exist in children whose arthritis extends, and this has implications for our understanding of disease and the design and timing of therapeutic interventions. (First Release Sept 15 2006; J Rheumatol 2006;33:2337–43)

Key Indexing Terms:
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Juvenile idiopathic arthritis (JIA) is an umbrella term for the inflammatory arthritides of childhood, a diverse group of conditions with differing prognoses. Children presenting with JIA who have a monoarthritis generally have a good prognosis in terms of their joint disease[1-4]. However, significant numbers of these children go on to develop arthritis in more joints, and these children have a worse prognosis[1]. The early introduction of second-line agents, such as methotrexate, has significantly improved the outcome of children with extensive arthritis[5]. In contrast, children with a persistent oligoarthritis often do well with nonsteroidal antiinflammatory drugs (NSAID) or intraarticular steroids[6,7]. Identifying children at highest risk of extension of arthritis at presentation would allow earlier aggressive management for those most at risk, without overtreatment of others. There are a few clinical associations with an increased risk of extended arthritis, but these may be of limited value when targeting early therapy, as many evolve over time[8,9].

Magnetic resonance imaging (MRI), ultrasound, and synovial biopsy have been shown to be more sensitive than clinical assessment in identifying subtle synovitis in adults[10-13]. They have been used to assess joints with normal, equivocal, or early clinical findings[12-18] and to evaluate cartilage integrity[14,16,19]. The potential of MRI with gadolinium enhanced sequences to identify subclinical changes predicting disease relapse has long been recognized[20]. The use of MRI and ultrasound in children with JIA is developing[21-26] with recognition that gadolinium enhanced images are the most sensitive, although ultrasound has many advantages in children[23].

From the Department of Child Health, Royal Hospital for Sick Children, Yorkhill; and Division of Developmental Medicine, University of Glasgow, Glasgow, and Birmingham Children's Hospital, Birmingham, United Kingdom.

J.M. Gardner-Medwin, MRCP, PhD, Senior Lecturer in Paediatric Rheumatology; O.G. Killeen, MRCPCH, Clinical Research Fellow, Division of Developmental Medicine, University of Glasgow and Birmingham Children's Hospital; C.A.J. Ryder, MRCP, Consultant Paediatric Rheumatologist; K. Bradshaw, MRCP, FRCR, Consultant Radiologist; K. Johnson, MRCP, FRCR, Consultant Paediatric Radiologist, Department of Child Health, Royal Hospital for Sick Children.

Address reprint requests to Dr. J. Gardner-Medwin, Department of Child Health, Royal Hospital for Sick Children, Yorkhill, Glasgow, G3 8SJ, UK. E-mail: jgm4w@clinmed.gla.ac.uk

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Ultrasound can identify inflammatory change in clinically normal joints in children[24] or adults[13] with inflammatory arthritis.

We examined the value of MR imaging of a single, clinically normal joint in children with a monoarthropathy, and followed their clinical progress to identify whether MR imaging is sensitive in detecting subclinical changes, and whether these MR features are predictive of the clinical course.

MATERIALS AND METHODS

Patients. Consecutive children presenting to a tertiary pediatric rheumatology center with a monoarthritis were invited to take part. Ten patients were recruited.

Summary of protocol. Two clinicians (JGM and CR) independently examined the children and agreed they had a monoarthritis. Each patient then had MRI of a clinically normal knee around the time of presentation, and repeated clinical examinations every 3–6 months recording all active and limited joints attributed to arthritis. The endpoint was the development of arthritis in a second joint. Table 1 gives the patients' characteristics.

Local ethics committee approval was given for this study.

Clinical assessment. Clinical examiners were blinded to the MR results. Consultant pediatric rheumatologists examined each child, and recorded all active and limited joints attributed to arthritis according to established criteria[27]. These criteria have been used within the clinic setting as part of routine clinical practice for many years, and all examiners were familiar with them. Two clinicians (JGM and CR) made a clinical assessment of the joints prior to imaging, confirming a monoarthritis. Thereafter CR was not blinded to the MR results, and his clinical assessments are not included in the analysis. At subsequent examinations JGM and at least one other consultant pediatric rheumatologist examined all cases. Musculoskeletal examination was repeated at 3–6 monthly intervals over a median of 37.0 (range 6.6–47.0) months to determine any change in active and limited joints. Features of their disease that might contribute to outcome were recorded at baseline [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor, HLA-B27, antinuclear antibodies (ANA); presence of uveitis, enthesitis, psoriasis or a family history of psoriasis, or HLA-B27 associated diseases]. Classification was done at the end of the study.

Clinical management. Management of the arthritis in each child was standardized. All (except one patient, where swelling spontaneously resolved by Day 35) received intraarticular triamcinolone hexacetonide (TH) into the presenting joint, given under general anesthetic, at a dose up to 2 mg/kg. NSAID were permitted. No patient received methotrexate or other second-line agents until they had developed arthritis involving 4 or more joints.

Radiological assessment. MR examinations were performed on the clinically unaffected contralateral knee, in all children. In those patients who presented with a joint other than the knee, the knee that was chosen for imaging was on the contralateral side to the presenting joint. Each patient had MR imaging soon after clinical presentation (Table 1). In 7 cases this was within 30 days of presentation. For 3 cases it was between 61 and 122 days after presentation.

All MR examinations were performed on a 1.5 Tesla system (Symphony; Siemens, Erlangen, Germany). The sequences used were proton-density fast-spin-echo (FSE), fat saturated (FS) sagittal [TR 1154 ms, TE 12 ms, 512 × 512 matrix, 214 × 214 mm field of view (FOV)]; proton-density FSE, FS coronal (TR 300 ms, TE 42 ms, matrix 175 × 256 mm and FOV 140 × 160 mm); proton-density axial FSE, FS (TR 300 ms, TE 42 ms, matrix 175 × 256 mm and FOV 140 × 160 mm); T2 spin-echo (SE) sagittal (TR 4000 ms, TE 96 ms, matrix 256 × 256 mm and FOV 150 × 150 mm); and T1 SE sagittal (TR 600 ms, TE 20 ms, matrix 384 × 512 mm and FOV 150 × 150 mm).

All children received coronal and sagittal postgadolinium DTPA (0.01 mmol/kg) T1 SE FS sequences. These postgadolinium sequences were performed within 1–2 minutes after injection of the contrast medium.

All MR examinations were reviewed independently by 2 consultant pediatric radiologists (KJ and KB), both with substantial experience in musculoskeletal MRI in children. The internal ligaments, soft tissues, synovium, cartilage, and bony structures were assessed to determine any features of arthritis. The radiologists were blinded to the clinical picture, and all the MR images were reviewed independently; if there was a discrepancy an agreement was subsequently reached by consensus. The families were blinded to all MRI findings.

Criteria for reporting the MR scans were developed from previous work[21,28]. Synovial thickness was measured on the sagittal postgadolinium T1 fat saturated images. Thickened synovium was defined as the synovium lining > 2 mm thick on 2 adjacent slices, or thickened on one slice and irregular on the other. A small amount of fluid in the center of the joint was regarded as normal. Fluid causing distension of the joint capsule, fluid beyond the menisci, or fluid in the suprapatellar bursa was regarded as abnormal. A smooth, regular infrapatellar fat pad was a normal finding, in contrast to any irregularity, which was not. Small unenhancing lymph nodes were classified as normal findings. If they were > 1 cm diameter or enhanced this was classified as abnormal.

Comparison of MRI to other predictors of disease extension. Studies have

Table 1. Patient characteristics.

	Whole Group	Normal MRI	Abnormal MRI	p
No. of patients	10	5	5	
Sex, M:F	3:7	1:4	2:3	1.00*
Mean age (range) at presentation, yrs	9.4 (5.2–14.2)	8.3 (5.2–14.2)	11.0 (7.7–13.0)	0.32***
Median duration of arthritis at presentation, days	89 (0–379)	77 (0–379)	16 (0–152)	0.62**
Uveitis	1	1	0	
Presenting joint				
Knee	8	4	4	
Elbow or ankle	2	1	1	
Final no. of affected joints at end of study	1–9	1	2–9	
Median time from first clinical assessment to MRI, days	39.0 (29–122)	31.0 (31–61)	61.0 (29–122)	0.75**
Median no. of blinded clinical assessments	6.0 (2–8)	5.0 (2–6)	7.0 (6–8)	0.023**†
Median length of followup after MRI, mo	37.0 (6.6–47.0)	29.5 (6.6–42.0)	40.0 (38–47)	0.594**
Median time after MRI to 2nd joint, mo		Never	3.9 (3.0–6.1)	

* Fisher's exact test. ** Mann-Whitney test. *** Student t test. † $p < 0.05$.

identified clinical features associated with an increased risk of developing arthritis in new joints[1,8,9]. We compared the value of MRI to these previously identified predictors (Table 2).

Statistics. Fisher's exact test and Mann-Whitney tests were performed as appropriate, using minitab t tests.

RESULTS

There were clear clinical associations with the MRI findings (Table 3).

Ten patients had MRI of clinically normal knees. For all 10 children there was no discrepancy in the imaging findings, and the 2 radiology observers showed 100% correlation in their findings.

Abnormal MR imaging. There were 5 children who had abnormal MR examinations in clinically normal knees (Figures 1A and 1B, and 3).

In 4 cases there was evidence of synovial hypertrophy that was more than 2.0 mm thick. This was seen in the suprapatellar bursae, infrapatellar, and centrally around the knee joint. There was no specific pattern to the involvement of synovium in each child. Synovial hypertrophy was associated with a joint effusion in all cases. In 2 cases there was enlarged, enhancing lymphadenopathy and in one child irregularity of the infrapatellar fat pad was seen.

All 4 of these patients still had a monoarthritis at the time of MRI, but developed arthritis in new joints a median of 3.9 (range 3.0–6.1) months later. Two patients had a diagnosis of persistent oligoarthritis at the end of the study; the only new joints to develop arthritis were the imaged knees, at 2.96 and 6.05 months post-MRI. They both have had recurrent problems in the affected joints, and are now at 3.5 and 3.1 years of followup. The third patient developed further arthritis (not in the imaged knee) within 6 months of the MRI, developing clinical arthritis in the imaged knee 11 months after the MRI changes were noted, and has 7 affected joints at 3.9 years of followup. The final case has never developed clinical arthritis in the imaged knee despite 3.8 years of followup, but has developed clinically apparent arthritis in a total of 9 other joints. Arthritis extended to other joints from the presenting knee 3 months after the MRI. MRI identified subtle effusions with synovial enhancement, but no lymphadenopathy.

An 8-year-old boy presented with a single swollen knee that resolved clinically within 35 days of onset without treatment. The MRI of the opposite unaffected knee was performed at 37 days, 2 days after this normal clinical examination, and was reported as equivocal (Figure 3). Both radiologists detected synovial thickening within the knee joint, but no other MR features of JIA. The synovial thickening was around 2 mm in depth and the radiologists were unsure of the significance of this single finding. There was no further clinical joint involvement upon 3 further examinations over a period of 8 months. This was attributed to reactive arthritis.

Normal MR imaging. In 5 patients the MRI was reported as normal (Figure 2), with the involved joint at presentation being the knee in 4 cases and the ankle in the fifth. Four of these patients clinically had JIA, with a persistent monoarthritis affecting the presenting joint only, over a median followup after MRI of 29.5 (range 6.6–42.0) months, during which time they had clinical examinations by a median of 5.0 (range 2–6) blinded examiners. Three of the 4 patients with knee involvement had persisting or recurrent episodes of inflammatory arthritis in the presenting knee over a further mean 7.3 (range 1.9–11.0) months after MRI, despite treatment with intraarticular steroids with or without NSAID. In one child the arthritis resolved with a single treatment of intraarticular steroids, and was still asymptomatic 36 months later. One boy aged 14.2 years was HLA-B27-positive, had never had enthesitis, and presented with arthritis in a single ankle. This did not extend to any further joints, and he only had clinical inflammation in the presenting ankle over a 2-month period. Normal MRI of a clinically unaffected knee was performed 1.9 months after the ankle had resolved clinically. He was followed for a further 42.0 months after the MRI and remained well. This was considered reactive arthritis.

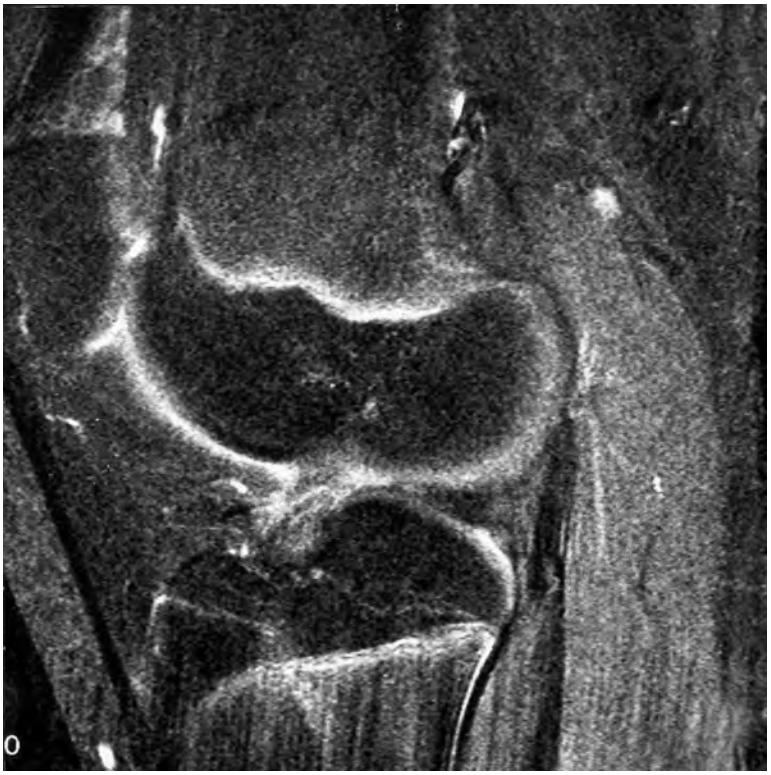
Known associations with extended arthritis. To determine if

Table 3. Clinical outcome versus MR findings. Sensitivity 100%, specificity 83%. Positive predictive value 80%, negative predictive value 100%.

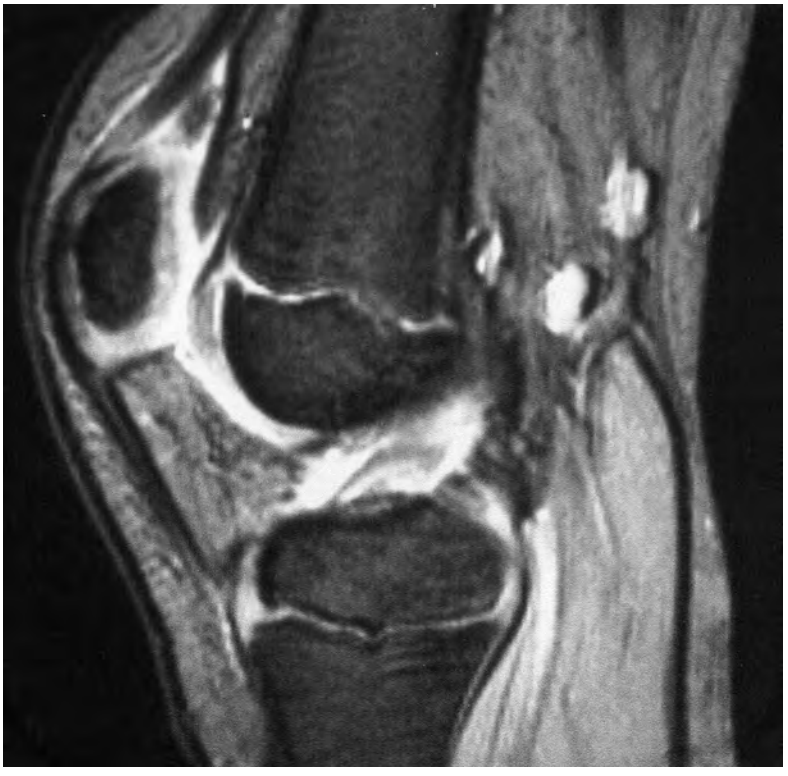
	Normal	Abnormal
Persistent monoarthritis	4	0
Arthritis > 1 joint	0	4
Reactive arthritis	1	1

Table 2. Clinical characteristics at presentation that have previously been determined to be associated with poor outcome.

Predictor	Indicator	All	Normal MRI	Abnormal MRI
ESR[1,9]	> 20 mm/h	0	0	0
	10–20 mm/h	3	2	1
Joint pattern [1,8,9]	Upper limb	1	1	0
	Ankle	1	1	0
Disease marker[8]	Psoriatic features	0	0	0
	HLA-B27	1	1	0
	Rheumatoid factor	0	0	0
DMARD[9] required by end of study		2	0	2



A



B

Figure 1. Sagittal T1 fat saturated postgadolinium post-DPTA images. A. There is enhancement anteriorly within the joint. There is also enhancement around the anterior cruciate ligament and in the suprapatellar bursae. These features were regarded as abnormal. B. There is abnormal enhancement anteriorly within the knee joint and also in the suprapatellar region. There is a small amount of enhancement posteriorly. There are 2 enhancing lymph nodes in the popliteal fossa. These features were regarded as abnormal.

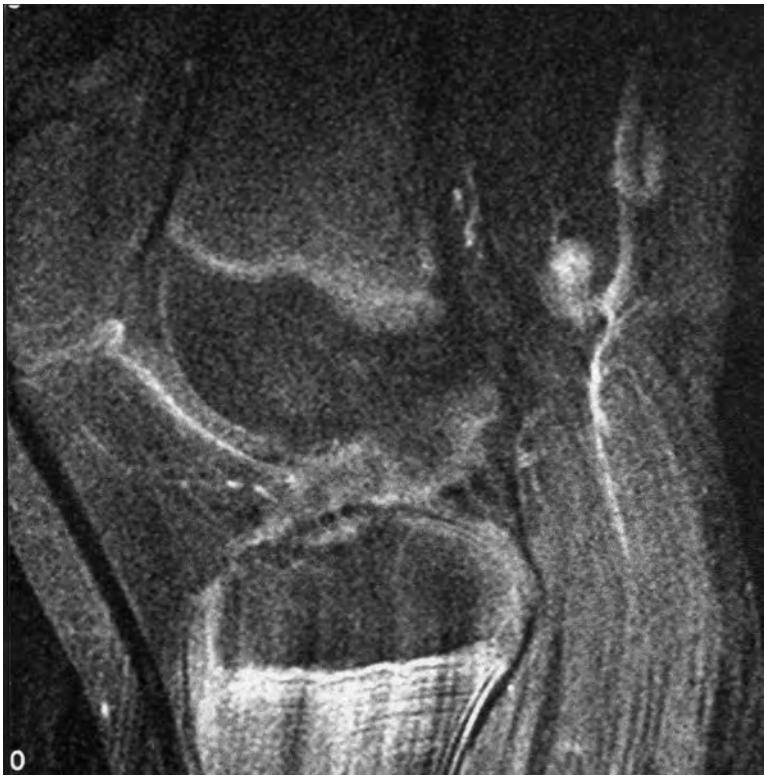


Figure 2. Sagittal T1 fat saturated postgadolinium post-DPTA image. There is very minor enhancement of the synovium in the anterior aspect of the knee joint between the femoral condyle and the infrapatellar fat pad. This was regarded as a normal finding.

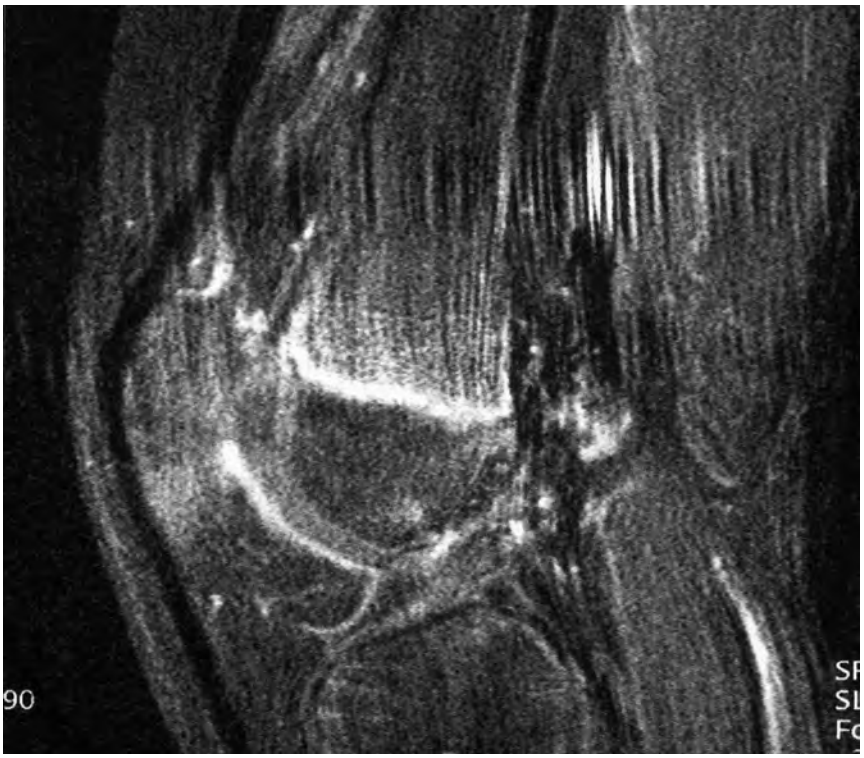


Figure 3. There is synovial enhancement in the anterior aspect of the knee joint adjacent to the infrapatellar fat pad. The outline of the synovial enhancement is slightly irregular and slightly thickened. The findings are of equivocal significance.

positive MR changes only identified patients who had previously described clinical risk factors for extension of arthritis, comparison was made with factors outlined in Table 2. No patient had an ESR > 20 mm/h, and CRP was normal in all patients. One patient had ankle involvement and was HLA-B27-positive, and a second patient had upper limb involvement. Neither of these patients developed polyarthritis or extended arthritis. Arthritis in more than 4 joints developed in 2 patients at 5 and 24 months after initial onset of disease, but abnormalities on the MRI were apparent in these 2 patients at presentation some 4 and 22 months earlier. Uveitis was present in only one patient with a persistent monoarthropathy and normal MRI.

DISCUSSION

Early introduction of disease modifying antirheumatic drugs (DMARD) in inflammatory arthritis is important in improving outcome[5,29,30], but predicting which patients require DMARD is difficult. MR and ultrasound are important tools in the early detection of inflammatory arthritis in adults[13,31] and children[24]. This pilot study has, for the first time, identified features on MRI of clinically normal knees in children with JIA that were predictive of the patient's clinical course. MRI distinguished between children with a persistent monoarthritis and those who developed clinically apparent arthritis in new joints up to a year later. MRI revealed subtle changes in the joints, including the synovium, in all the cases that subsequently extended, but in none of those that did not. This raises the possibility of 2 different disease processes: patients who ultimately develop more than one affected joint have MR changes consistent with synovitis without the clinically affected joint, which might hypothetically be generalized, affecting a larger number or even all joints from the onset. In contrast a "true" monoarthritis appeared to be characterized by a lack of MR changes in an unaffected joint, and the disease process seemed to be a monoarthritis from the start. While this is a new concept, differing from previously described disease patterns in JIA, we are aware of the small numbers in this preliminary study. A larger study investigating this concept further and in larger numbers is under way. The concept of a widespread inflammatory process versus one confined to a single joint was not supported by the finding of uveitis in only one patient, who had a persistent monoarthritis. MRI was not able to distinguish the traditional division of children who have persistently limited joint involvement (< 4 joints or persistent oligoarthritis) from those who developed a polyarthritis (extended oligoarthritis or polyarthritis). However, the results do suggest a widespread inflammatory process may exist in children whose arthritis extends beyond one joint, and this has implications for our understanding of disease, and the design and timing of therapeutic interventions.

We chose to image a normal knee because we considered it a comparatively easy joint to assess clinically. When designing the study we also felt it was important to choose a joint with a high probability of developing arthritis during the followup period. However, in one child MR changes were associated with extension of arthritis to many joints, although the imaged knee remains clinically normal nearly 4 years later. In another patient arthritis developed in other joints at 3 months, whereas the imaged knee remained clinically normal for nearly a year. This raises the possibility that the MR features in patients who develop extended disease are a widespread articular phenomenon, analogous to adults[13], and we now wish to investigate MR changes in joints at a lower risk of developing arthritis to examine this further.

MRI has been found to be a sensitive and accurate tool in rheumatoid arthritis[32,33]. In this small pilot study the MR imaging was both sensitive and specific. In only one case did both radiologists identify equivocal MRI results as looking different from those of the patients with JIA, and in this case the child had a resolving reactive arthritis. Both radiologists were readily able to identify this case as different. For all the abnormal examinations the radiologists were confident in their diagnosis without disagreement in their findings. This would suggest that the detection of subclinical disease on MRI would not be a difficult undertaking for a suitably trained radiologist, which improves the clinical usefulness of such examinations.

The MR findings in those children with extending disease were consistent, identifying small joint effusions, synovial hypertrophy, lymph node enhancement, irregular infrapatellar fat pads, and marrow edema as the abnormal features. In this small study we did not have the patient numbers or combinations of disease to reveal additional features that might have contributed to the identification of disease types such as enthesitis, or erosions, or to determine how these findings relate to the current classification of JIA[34]. However, MRI is established as an accurate way to identify enthesitis, tenosynovitis[35-37], and erosions[31,38] in adults, and larger numbers might be helpful in determining disease type, as another prognostic indicator in children.

The previously described associations with risk of disease extension were shown to be unhelpful in these patients. As commonly found in children with oligoarthritis (and notably different from a similar ultrasound study in adults[13]), no patient in our study had a significantly elevated ESR (i.e., > 20 mm/h), and those with marginally raised ESR (10–20 mm/h) were evenly distributed in both the extending and non-extending groups. Other associations with extended disease such as joint pattern, psoriatic markers, HLA-B27, or rheumatoid factor were not useful in predicting extension in this group.

A larger study is in progress to confirm these findings, exploring the comparative value of ultrasound and MRI, and the development of changes on MRI as clinically apparent arthritis develops. Clinical examination is known to be less sensitive than MRI in adults and children[39]. We hope also to explore the variability in clinical assessment of the joints between clinicians in order to provide evidence that our clini-

cal skills here were no less sensitive than most.

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