

Original article

Dynamic contrast-enhanced magnetic resonance imaging in the assessment of disease activity in patients with juvenile idiopathic arthritis

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Abstract

Objective. To determine the capability and reliability of dynamic contrast-enhanced MRI (DCE-MRI) in the assessment of disease activity in juvenile idiopathic arthritis (JIA).

Methods. DCE-MRI of the clinically more affected wrist or hip joints was undertaken in 21 patients, coupled with standard clinical assessment and biochemical analysis. Synovial inflammation was assessed by computing the maximum level of synovial enhancement (ME), the maximum rate of enhancement (MV) and the rate of early enhancement (REE) from the enhancement curves generated from region of interest independently delineated by two readers in the area of the ME. Correlations between dynamic parameters and clinical measures of disease activity, and static MRI synovitis score were investigated.

Results. In patients with wrist arthritis, REE correlated with the wrist swelling score ($r_s=0.72$), ESR ($r_s=0.69$), pain assessment scale ($r_s=0.63$) and childhood HAQ ($r_s=0.60$). In patients with hip arthritis, ME correlated with the hip limitation of motion ($r_s=0.69$). Static MRI synovitis score based on post-gadolinium enhancement correlated with MV ($r_s=0.63$) in patients with wrist arthritis and with ME ($r=0.68$) in those with hip arthritis. The inter-reader agreement assessed by intra-class correlation coefficient (ICC) for ME, MV and REE (ICC=0.98, 0.97 and 0.84, respectively) was excellent.

Conclusions. DCE-MRI represents a promising method for the assessment of disease activity in JIA, especially in patients with wrist arthritis. As far as we know, this study is the first to demonstrate the feasibility, reliability and construct validity of DCE-MRI in JIA. These results should be confirmed in large-scale longitudinal studies in view of its further application in therapeutic decision making and in clinical trials.

Key words: MRI, Dynamic contrast enhancement MRI, Juvenile idiopathic arthritis, Disease activity.

Introduction

Juvenile idiopathic arthritis (JIA) represents a group of heterogeneous diseases characterized by a chronic inflammatory process primarily targeting the SM. A persistent synovitis is associated with an increased risk

of osteocartilaginous damage and physical functional disability [1]. Modern therapeutic strategies are aimed at an early control of inflammatory process in order to prevent joint damage. As novel and highly effective treatments are now available for treating JIA [2–4], demand has been created for new imaging techniques that are able to provide objective and accurate measures for the detection of joint inflammatory changes and for monitoring treatment response. Conventional radiography, which is the current standard for the assessment of joint damage in JIA, is quite insensitive in depicting soft tissue changes, including synovitis, as well as in detecting the earliest stages of erosive changes. One distinct advantage of MRI over plain radiography is its ability to image soft

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Submitted 12 May 2009; revised version accepted 24 September 2009.

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tissues, as well as early bony changes. Enhancement of MRI with paramagnetic contrast agents, such as gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA), allows direct visualization and measurement of the inflamed SM [5]. The technique of dynamic contrast-enhanced MRI (DCE-MRI) provides a quantitative assessment of inflammation based on the analysis of the time course of signal changes following gadolinium injection. The rate of enhancement of the synovial compartment is mainly determined by the local tissue vascularity and by the capillary permeability, both of which are supposed to closely mirror the degree of inflammatory activity [6, 7]. Indeed, the rate and magnitude of synovial enhancement provided by DCE-MRI have proven of value in assessing disease activity [8] evaluating response to treatment [9, 10], and predicting erosive progression in adults with RA [11, 12].

The main purpose of the present study was to determine whether the time-dependent changes in signal intensity of the SM on Gd-DTPA-contrasted images reflect the severity of synovial inflammation and are a valuable marker of disease activity in children with JIA. To the best of our knowledge, no other reports on the use of this technique in the study of the wrist and hip of children with JIA have been published.

Patients and methods

Patients who fulfilled the ILAR revised criteria for the diagnosis of JIA [13] and wrist or hip active arthritis were recruited from the study unit between June 2006 and October 2006. The clinically more affected joint was investigated with DCE-MRI. Patients with contraindications to MRI or requiring sedation to perform the exam were not included in the study. The study was approved by the local ethics committee (Ethics Committee of the Institute 'Giannina Gaslini', Genoa), and written informed consent was obtained from the parents of the children involved in this study.

Clinical assessment included count of joints with swelling, pain on motion/tenderness and restricted motion; physician's global assessment of overall disease activity measured on a 10-cm visual analogue scale (0 = no activity and 10 = maximum activity); assessment of functional ability, using the childhood HAQ (C-HAQ; 0 = best and 3 = worst) [14, 15]. In addition, a more

detailed scoring of the imaged joints was performed. Swelling and tenderness were graded from a minimum of 0 to a maximum of 3, whereas limitation of motion was graded from 0 to 4 [16]. The laboratory assessment of JIA activity included the Westergren ESR and the CRP level. All clinical assessments were performed on the same day of DCE-MRI by a paediatric rheumatologist (S.V.) with >20 years of clinical experience, who was blinded to the results of imaging investigations.

DCE-MRI and image processing

MRI was performed on a 1.5 Tesla MR scanner (Achieva Intera; Philips Medical Systems, Best, The Netherlands) using a Sense Flex Small Coil for the wrist, and a Sense Body Coil for the hip. A 3D FFE dynamic sequence was acquired before and after intravenous contrast injection of 0.1 mmol/kg of Gd-DTPA (Magnevist; Schering, Berlin, Germany): after a first volume acquisition, contrast agent was administered using a power injector (at a flow rate of 2 ml/s) through a 22-gauge cannula inserted into a cubital vein. Each volume was acquired every 5 s, for a total of 40 3D datasets. Pre-contrast image was subtracted from all subsequent images of the dynamic study in order to increase the conspicuity of enhancing synovitis. After dynamic imaging, static post-contrast 2D coronal TSE T1w images were obtained. The detailed imaging parameters of MR scanning are outlined in Table 1. Image analysis was performed by two operators (C.B. and A.V.), with 3 and >10 years of experience in the field of biomedical image analysis, respectively, using a software developed in house.

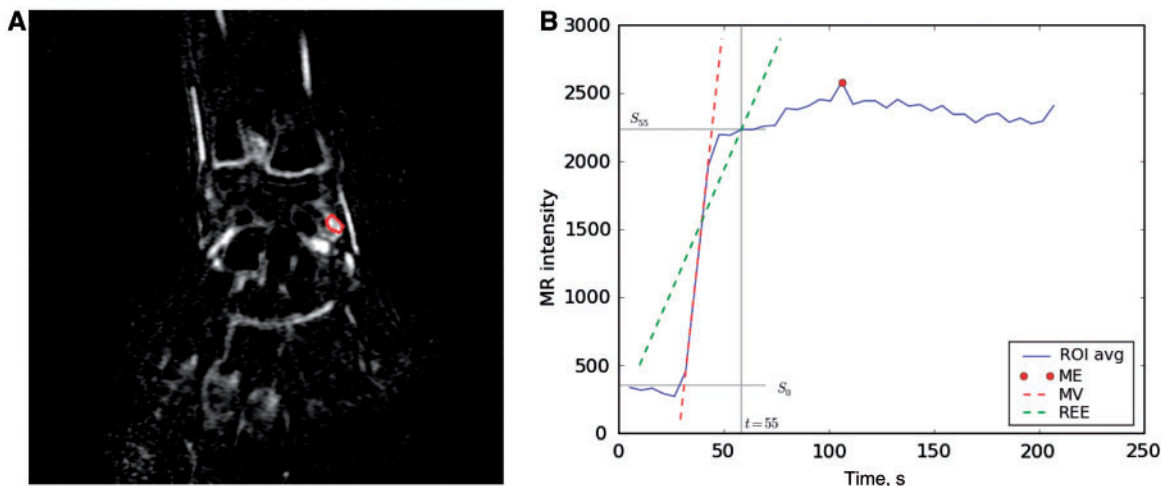
The images were processed blinded to the clinical and laboratory findings. The rate of enhancement was calculated over a region of interest (ROI) independently drawn by two operators in the area of maximal visual synovial enhancement (Fig. 1A). The two operators were a paediatric radiologist (M.B.D.) and a paediatric rheumatologist (C.M.) with 3 years of experience in reading of MR images. In order to help placing the ROIs, the image of the maximum intensity projection (MIP) over time has been automatically computed. The MIP is a static 3D image where the maximum intensity reached during the whole acquisition is assigned to each voxel. Enhancement curves were obtained plotting the mean pixel intensities of the ROI against the time following gadolinium injection. Signal enhancement time course

TABLE 1 MRI protocol

Sequence	Repetition time, ms	Echo time	Turbo factor	Number of sample averages	Matrix	Slice thickness/spacing, mm
Coronal TSE T1	600	22	3	3	205a/336 r	4/0.4
Axial TSE T1	600	22	3	3	205a/336 r	3/0.3
Coronal TSE PD/T2 fat saturation	1008	7.3/80	14	4	179a/7512 r	3/0.3
Coronal T1 FFE 3D dyn FA 40 (40 vol)	6	1.7		1	109a/320 r	1.5
T1TSE fat saturation CM	600	22	3	3	205a/336 r	3/0.3

TSE: turbo spin echo; FFE: fast field echo; PD: proton density; dyn: dynamic; CM: contrast medium; FA: flip angle.

Fig. 1 (A) MIP from a wrist MRI of a JIA patient. The MIP is a static 3D image in which to each voxel is assigned the maximum intensity reached during the whole acquisition. The ROI (in red) is drawn by the operator in the area of highest visual enhancement. **(B)** Dynamic enhancement curve following the injection of gadolinium. The curve, shown in blue, is obtained from the ROI. The ME reached during the acquisition is marked by a red circle. The MV and the REE are shown as dashed line, in red and green, respectively. The latter is defined as the curve slope in the first 55 s. S_0 : signal intensity before injection of Gd-DTPA; S_{55} : signal intensity 55 s after injection. See 'Patients and methods' methods section for details on the computation of ME, MV and REE.



has been studied in terms of maximum absolute enhancement (ME), which was calculated as follows: $ME = \max(S_i - S_0)$, where S_0 and S_i are the signal averages before and t_i seconds after the contrast injection; maximum rate of the enhancement (MV) was calculated according to the formula: $MV = \max(S_{i+1} - S_{i-1}) / (t_{i+1} - t_{i-1})$; and rate of early enhancement (REE) per second during the first 55 s using the formula $REE_{55} = (S_{55} - S_0) / (S_0 \times 55) \times 100\%$ (Fig. 1B). Evaluation of the enhancement after 55 s was deliberately chosen due to the results of a previous study on RA patients, where it was shown to allow good discrimination between knees with clinically active and inactive arthritis [17].

Synovitis grading scores were also obtained from static MR images by a paediatric musculoskeletal radiologist (P.T.) with >20 years of experience in reading of MR images and familiar with MR scoring system, who was blinded to the clinical data, as well as to the DCE-MRI findings. Synovitis was scored on the basis of synovial thickening (0 for <2 mm; 1 for 2–4 mm; 2 for ≥ 4 mm) and visual intensity of the synovium enhancement post gadolinium (0 for none, 1 for mild to moderate and 2 for gross) [18].

Statistical methods

Comparison of quantitative variables between patients with wrist and hip involvement was performed by the non-parametric Mann–Whitney U-test. The reliability and construct validity of DCE-MRI were analysed to provide a preliminary validation procedure of the technique as a tool for the assessment of the disease activity in JIA [19]. Inter-observer agreement for ME, MV and REE were analysed by computing the intra-class correlation

coefficient (ICC) [20], and agreement was classified as follows: $ICC < 0.4$ = poor; ≥ 0.4 – 0.8 = moderate; and ≥ 0.8 = good agreement [21]. The independent scores of the two observers were then averaged, and this average was used for analyses. Correlations between quantitative parameters were assessed using Spearman's rank correlation coefficient (r_s), and P -values < 0.05 were considered as statistically significant. Statistical analysis was performed with Statistica (StatSoft, Tulsa, OK, USA).

Results

A total of 22 patients (8 males and 14 females) were included in this cross-sectional study. Twelve patients had active wrist arthritis and 10 patients had active hip disease. The demographic and clinical features of the patients are summarized in Table 2. Patients with wrist arthritis showed a significantly higher number of active joints and significantly greater disease activity, as assessed by the physician's visual analogue scale (VAS), compared with patients with hip arthritis ($P < 0.001$ and < 0.01 , respectively). Laboratory findings, functional ability and clinical parameters of damage, as well as disease duration, were similar in the two groups. Drug treatment was also similar, with the exception of oral corticosteroids, which were more frequently used in patients with hip arthritis.

DCE-MRI of the clinically more affected wrist (12 patients) or hip joints (10 patients) was undertaken without causing any discomfort or adverse events. As far as dynamic parameters are concerned, ME and MV values were significantly higher ($P < 0.001$) in patients

TABLE 2 Demographic features and results of the clinical and laboratory assessment of the 22 patients enrolled

	Patients with wrist active arthritis, <i>n</i> = 12	Patients with hip active arthritis, <i>n</i> = 10
No. of males/no. of females	2/10	6/4
Systemic arthritis, <i>n</i> (%)	3 (25)	6 (60)
RF-negative polyarthritis, <i>n</i> (%)	1 (8.3)	
RF-positive polyarthritis, <i>n</i> (%)	1 (8.3)	
Oligoarthritis, <i>n</i> (%)		
Extended	5 (41.7)	1 (10)
Persistent	1 (8.3)	1 (10)
Entesitis-related arthritis, <i>n</i> (%)		1 (10)
Undifferentiated, <i>n</i> (%)	1 (8.3)	1 (10)
Age at study visit, mean (s.d.), years	11.7 (3.9)	12.9 (4.2)
Disease duration, mean (s.d.), years	6 (3.9)	6.6 (4.9)
Number of active joints, mean (min–max)	11 (3–28)	2 (0–5)
Number of swollen joints, mean (min–max)	7.3 (0–18)	0.8 (0–3)
No. of joints with LOM, mean (min–max)	7.2 (2–29)	4.8 (0–6)
VAS-PGA, mean (min–max)	6.9 (0–10)	3.02 (0–8.4)
Local score pain, mean (min–max)	1.7 (1–3)	0.7 (0–2)
Local score swelling, mean (min–max)	1 (0–2)	
Local score LOM, mean (min–max)	1.9 (0–3)	1.4 (0–4)
CHAQ score, mean (min–max)	0.56 (0–1.125)	0.24 (0–0.875)
Pain intensity, mean (min–max)	3.5 (0.1–9)	2.4 (0–9.6)
CRP, mean (min–max), mg/dl	4.8 (0.5–19.2)	2.2 (0.5–6.7)
ESR, mean (min–max), mm/h	35.4 (5–85)	24.5 (2–43)
NSAID, <i>n</i> (%), months (mean) ^a	7 (58.3), 9.8	4 (40), 12.4
Oral corticosteroid, <i>n</i> (%), months (mean) ^a	2 (16.7), 8	5 (50), 12.2
MTX, <i>n</i> (%), months (mean) ^a	8 (66.7), 71.5	4 (40), 55.7
Cyclosporin A, <i>n</i> (%), months (mean) ^a	1 (8.3), 9	1 (10), 12
Etanercept, <i>n</i> (%), months (mean) ^a	4 (33.3), 27.3	4 (40), 48.2
Kineret, <i>n</i> (%), months (mean) ^a		2 (20), 18

Values in bold differ significantly between the two groups of patients. ^aMonths (mean): the mean time, in months, between the start of therapy and the DCE-MRI. VAS-PGA: physician's global assessment of overall disease activity.

with wrist arthritis than in those with hip disease, as shown in Fig. 2.

Correlation between DCE-MRI measurements and clinical findings

In order to preliminarily investigate the construct validity of DCE-MRI as a method for the assessment of the disease activity in JIA, we have looked for relationships between dynamic parameters and other measures that evaluate the same phenomenon, such as conventional clinical measures of disease activity and semiquantitative synovitis scores as assessed on static MR images.

In patients with wrist arthritis, REE was highly correlated with conventional measures of disease activity, such as the wrist swelling score and ESR ($r_s = 0.72$; $P < 0.02$ and $r_s = 0.69$; $P < 0.02$, respectively) and moderately correlated with the pain intensity and functional ability, as assessed by the C-HAQ score ($r_s = 0.63$; $P < 0.05$ and $r_s = 0.60$; $P < 0.05$, respectively). Furthermore, REE, ME and MV did not correlate with clinical damage indicators, such as the severity of the wrist limitation of motion score, and the count of joints with restricted motion. In patients with hip active arthritis, ME was correlated with the

severity of the limited range of motion (LOM) ($r_s = 0.69$; $P < 0.05$).

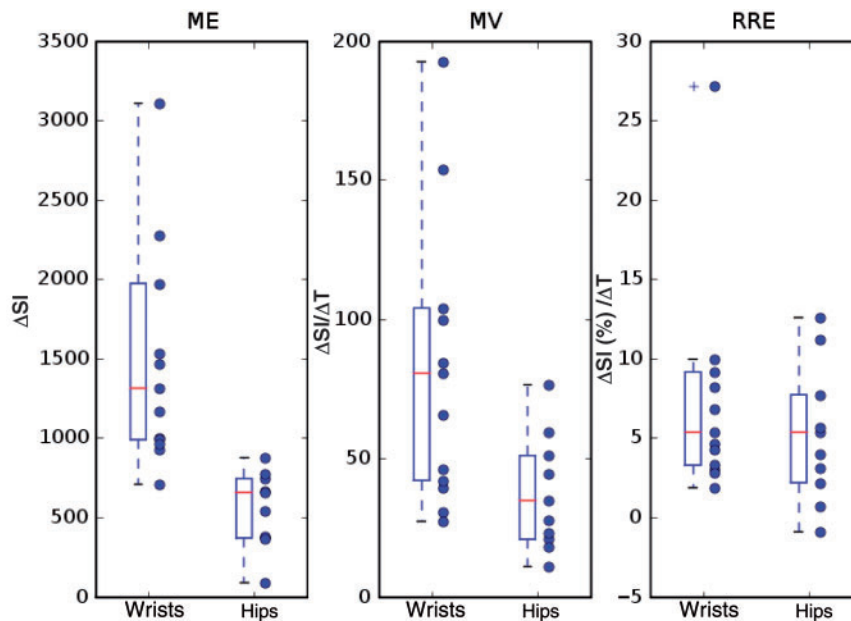
Correlation between MRI dynamic parameters and MRI static synovitis scores

Synovitis from dynamic scans was compared with synovitis assessed on static MRI scans taken at the same time. The semiquantitative synovitis score based on the visual intensity of the synovial enhancement from static MR images was significantly correlated with MV ($r_s = 0.63$; $P < 0.05$) in the patients with wrist arthritis, and with ME ($r_s = 0.68$; $P < 0.05$) in the patients with hip involvement. No correlations were found between static synovitis score based on synovial thickening and the dynamic parameters.

Reliability

The reproducibility of the dynamic parameters was assessed for the enhancement curves obtained from the ROIs, independently placed by the two observers. The inter-observer agreement, as assessed by the ICC, for ME (ICC = 0.98; 95% CI 0.89, 0.99), MV (ICC = 0.97; 95% CI 0.85, 0.99) and REE (ICC = 0.84;

Fig. 2 Values of ME, MV and RRE in patients with JIA and wrist or hip involvement. Both the individual values (circles) and the box plots of the three quantities are shown. In the box plots, the median values are indicated by a horizontal dash and the rectangular boxes extend from the lower to the upper quartiles. Whiskers extend from the box to show the range of the data; outliers are shown with a plus sign. SI: signal intensity; T: time (s).



95% CI 0.66, 0.93) was excellent. These results indicate that synovial inflammatory activity can be reliably assessed by DCE-MRI.

Discussion

The advent of new effective structure-modifying treatment for JIA and the trend towards early suppression of inflammation to prevent erosive disease shifts the emphasis away from conventional radiography detectable structural damage to early-stage manifestations of the disease, and drives the need for alternative imaging techniques to be more sensitive for detecting inflammatory changes in the soft tissues and monitoring treatment effect.

DCE-MRI has shown to be a sensitive and accurate method for estimating synovitis in RA [8, 22–24], monitoring response to therapy [25–27], as well as for predicting future bone damage [11, 12].

In contrast to the many studies performed in adults, to the best of our knowledge no studies on the assessment of synovitis in JIA using DCE-MRI of the wrist and hip joints have been reported. Workie *et al.* [28, 29] recently proposed a pharmacokinetic modelling to quantify signal-enhancement curves of dynamic Gd-DTPA imaging of the knee in JIA, and suggested that pharmacokinetic parameters are potentially useful for quantitative monitoring of the disease activity and response to therapy. Although the knee is the most commonly affected joint in JIA, in our study, wrist and hip joints were chosen because of the prognostic value of their involvement. McQueen *et al.* [30], in fact, demonstrated that wrist

MRI may be useful in predicting whole-body radiographic outcome in RA patients.

Some of the most compelling proofs that DCE-MRI might represent as a good marker for disease activity assessment in RA come from comparative studies with histology, showing that the enhancement rate and the overall histopathological signs of synovial inflammation are closely correlated [7, 9, 10, 31]. Since in JIA there is no available 'gold standard' for the determination of disease activity to which to relate DCE-MRI results, its construct validity was preliminarily investigated. Overall, the significant correlations between the dynamic parameters and the static MR measures of the enhancement, and a reasonable agreement with standardized clinical measures of disease activity gave supportive, preliminary evidence for construct validity of DCE-MRI for assessing disease activity in JIA, especially in patients with wrist arthritis.

The absence of a significant correlation between dynamic parameters and clinical markers of inflammation in patients with hip involvement is hardly surprising. In the present study, patients with hip disease had lower levels of disease activity according to dynamic parameters compared with patients with wrist arthritis, and it may be possible that low levels of inflammation can not be adequately captured by clinical examination. Previous studies, in fact, highlighted the inadequacy of clinical examination concerning its ability to reveal disease activity in hip joints, and the risk for a progression of the structural damage despite clinically adequate control of the disease [32–35].

Despite the standardized DCE-MRI acquisition protocol, technical issues (e.g. different coils used and the depth of the joint from the coil) and specific differences in synovitis among different joints should be also considered; a marked IA inflammatory heterogeneity within large joint of RA patients has been described [25, 36, 37]. It could be hypothesized that synovial inflammation could be more homogeneous in the wrist than in the hip; this likely accounts for the differences between the dynamic parameters in the two groups of patients. The poor correlation with clinical parameters could be finally seen in the light of the small sample size and of the focal nature of the DCE-MRI examination. Because of inhomogeneity of inflammatory changes within SM of the larger joints, more accurate information about hip inflammation may be achieved by providing an overview of the tissue behaviour calculating enhancement rate from several ROIs. Previous studies, in fact, suggested that combining multiple small ROIs improves results [8, 22].

In the present study, dynamic measures of synovitis were correlated, as expected, with static MRI semiquantitative synovitis score based on visual enhancement, and not on synovial thickening. It is well known that the amount of synovial thickness is not necessarily related to the degree of disease activity; in fact, patients with longstanding disease might show a thick SM but with low enhancement, mainly due to the gradual replacement of hypervascular pannus by fibrous tissue [38, 39].

In keeping with findings of previous studies [10, 11, 40], also in JIA patients with wrist arthritis, the REE showed higher correlations with clinical and laboratory features compared with the other dynamic parameters. In contrast, ME and MV showed better correlation with static synovitis semiquantitative score. Further studies are required in order to establish which dynamic parameter provided more information on the inflammatory activity of the SM, and to determine whether the REE, MV and ME indicate the same or different aspects of inflammation in the arthritic joint.

Only a few reports consider the reproducibility of DCE-MRI measurements, which is of critical concern if a wider application of this technique is considered. Huang *et al.* [11] found that the placement of the ROI at the highly enhanced areas could greatly affect the result of dynamic study, focusing the attention on the subjectiveness of the choice of the brightest region on the slice showing most enhancement. In the present study, the inter-observer agreement for the dynamic parameters was excellent, providing a preliminary evidence that DCE-MRI is a reliable instruments for the assessment of synovitis in JIA. We feel that the high reproducibility might have been facilitated by placing the ROI on the image automatically synthesized, with the voxels highest intensities over time (MIP). This allows the difference between high- and low-inflamed SM to be highlighted, facilitating the observer in selecting the appropriate tissue and site for analysis, and ensuring high reproducibility of the results.

In summary, DCE-MRI shows remarkable promise as a reliable and accurate tool for quantitative assessment of synovial inflammation and disease activity in JIA, especially in patients with wrist arthritis; it may have an important role in monitoring treatment efficacy, allowing a direct measurement of anti-inflammatory activity to be made. The results of our study must be interpreted within the limits of the pilot study design. DCE-MRI value for the assessment of hip inflammation remains to be determined in larger studies, with a broader spectrum of disease severities. The validation analysis was cross-sectional and therefore the predictive value relative to joint damage, as well as the sensitivity of DCE-MRI in detecting inflammatory changes in response to treatment remains to be examined in longitudinal studies; this is crucial before DCE-MRI could be used to guide therapeutic decisions or as an endpoint in therapeutic clinical trials.

Rheumatology key messages

- Accurate assessment of disease activity is crucial for the management of patients.
- Wrist DCE-MRI represents a promising and reliable method for the assessment of disease activity.
- Hip DCE-MRI value remains to be determined.

Acknowledgement

We wish to acknowledge the technical staff of the Radiological Department of the G. Gaslini Institute who supervised the MRI scans.

Funding: Supported by a grant from the European Union, Health-e-Child Integrated Project (IST-2004-027 749).

Disclosure statement: The authors have declared no conflicts of interest.

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