

Synovial and inflammatory diseases in childhood: role of new imaging modalities in the assessment of patients with juvenile idiopathic arthritis

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

With the advent of effective structure-modifying treatment for JIA, it may be possible to significantly reduce or even completely prevent structural damage and associated functional disability. The trend towards early suppression of inflammation, in order to prevent erosive disease, shifts the emphasis away from conventional radiographic detectable structural damage to the slightest traces of early joint damage, and drives the need for alternative imaging techniques more sensitive in detecting early signs of disease activity and damage. In this regard MRI and US are playing an increasing role in the evaluation of arthritic joints.

This article will review the key aspects of the current status and recent important advances of imaging techniques available to investigate the child with rheumatic disease,

briefly discussing conventional radiography, and particularly focusing on MRI and US. In this era of advancing imaging technology, knowledge of the relative values of available imaging techniques is necessary to optimize the management of children with JIA.

Keywords Bone · Joint · Arthritis · US · MR · Child

Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood and an important cause of short-term and long-term disability. Studies in developed countries have reported a prevalence that ranges between 16 and 150 per 100,000 [1]. The affected joints develop synovial proliferation and infiltration by inflammatory cells, with subsequent increased secretion of synovial fluid and pannus formation. Persistent synovial inflammation may ultimately lead to articular cartilage and bone damage that are responsible for most disability in JIA [2, 3]. JIA is not a single disease, but a term that encompasses all forms of arthritis with onset in patients <16 years old, lasting more than 6 weeks and of unknown origin. The term represents, therefore, a diagnosis of exclusion and a wide range of differential diagnoses, many of which have recognisable features on imaging (Table 1) [4].

A number of classification systems have been developed over the years, the most recent being that proposed by the International League of Association for Rheumatology (ILAR) (Table 2) that aims to enable identification of homogeneous groups of children suitable for aetiopathogenetic studies [5].

Imaging in JIA is crucial for diagnosis of the disease, assessing its severity and prognosis, monitoring disease

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Table 1 Differential diagnoses of arthritis in children**Inflammatory**

Inflammatory disease: inflammatory bowel disease, sarcoid

Malignancies: leukaemia, lymphoma, neuroblastoma

Infection: septic arthritis, osteomyelitis, tuberculosis, Lyme arthritis

Systemic disease: systemic lupus erythematosus, vasculitis, juvenile dermatomyositis, systemic sclerosis

Chronic recurrent multifocal osteomyelitis

Transient joint effusion/synovitis

Mechanical

Trauma: accidental and nonaccidental injury

Osteochondroses

Avascular necrosis and other degenerative disorders: Perthes, slipped upper femoral epiphysis, idiopathic chondrolysis

Inherited: skeletal dysplasias, congenital dislocation of the hip

Collagen disorders: e.g., Ehlers–Danlos, Marfan, Stickler syndromes

Tumours of cartilage bone or muscle:

Benign: osteoid osteoma, pigmented villonodular synovitis, haemangioma, lipoma arborescens

Malignant: synovial sarcoma, osteosarcoma, rhabdomyosarcoma

Inherited metabolic disorders: hypophosphataemic rickets, hypo/hyperthyroidism, diabetes, purine metabolism

Storage disorders e.g., mucopolysaccharidoses/lipidoses

Haematological: haemophilia and haemoglobinopathy (sickle cell disease predominantly)

Chronic infantile neurological cutaneous and arthritis syndrome (CINCA)

Idiopathic pain syndromes

Local: reflex sympathetic dystrophy

Generalized: fibromyalgia

progression and treatment response, and evaluating complications associated with the disease or its therapy. The recent introduction of effective structure-modifying treatments has created new demands on imaging for more sensitive methods of predicting and monitoring treatment effect [6, 7].

This article will review key aspects of the current status and recent important advances in imaging in JIA, briefly discussing conventional radiography, and particularly focusing on MRI and US. The value and limitations of these imaging modalities and an overview of future imaging scenarios in JIA will be also reported.

Advances in radiography

Up to the present day, conventional radiography (CR) has been the mainstay of imaging evaluation in JIA. The main radiological features in JIA are reported in Table 3, together with the advantages and drawbacks of this technique. The recent advances in radiographs in JIA can be summarized into two broad categories: technical advances and advances in the standardization of radiographic methods.

New computed radiography and digital/direct radiography, with electronic display and interpretation, have largely replaced films/screen radiography. Clinical studies in

patients with rheumatoid arthritis (RA) have demonstrated that the image quality of computed radiography is at least as good as screen-film; small and early erosions, in fact, can be seen equally well with the digital technique as compared with the conventional film-screen techniques [8, 9]. These results support diffusion of digital technique into clinical practice, with advantages also in image distribution, storage, and cost. Furthermore Ludwig K et al. [10], in a recent experimental study, have clearly demonstrated that a digital flat-panel detector offers a diagnostic performance superior to screen films, even in the detection of very small bone erosions (diameter starting from 0.5 mm, with a depth of 0.5 mm) at clinical exposure settings. According to the authors' conclusions, using the flat-panel system, the exposure dose can be reduced by 50% to obtain a diagnostic performance comparable with a speed class 200 screen-film.

Modern therapeutic strategies have created a growing need for a reliable radiographic assessment standard for evaluation of the potential value of these drugs in preventing structural joint damage in JIA. Assessment of structural damage is a key outcome endpoint in treatment efficacy studies and is now required by the US Food and Drug administration as a measure of disease progression in clinical trials of potential disease modifying antirheumatic drugs (DMARDs) in patients with RA [11]. The imaging evaluation of articular disorders in children differs from that

Table 2 Classification of JIA according to ILAR revised criteria

JIA subtype	Frequency ^a	Sex ratio and onset age
Systemic arthritis Diagnosis requires the presence of arthritis accompanied or preceded by quotidian fever of at least 2-week duration plus one or more of the following: typical evanescent erythematous rash, hepatomegaly or splenomegaly, generalised lymphadenopathy, or serositis.	4–17%	F=M Throughout childhood
Oligoarthritis Four or fewer joints affected during the first 6 months of disease -persistent oligoarthritis: the disease is confined to four or fewer joints throughout the disease course -extended oligoarthritis: arthritis extends to >4 joints after the first 6 months of the disease.	27–56%	F>>>M Early childhood
Rheumatoid factor (RF) positive polyarthritis Five or more joints affected during the first 6 months of disease, in the presence of IgM RF on at least two occasions more than 3 months apart.	2–7%	F>>M Late childhood or adolescence
Rheumatoid factor negative polyarthritis Five or more joints affected during the first 6 months of disease, in the absence of IgM RF.	11–28%	F>>M; biphasic distribution; early peak at 2–4 years and later peak at 6–12 years
Enthesitis-related arthritis Association of enthesitis and arthritis. Most children are HLA-B27 positive or have family history of HLA B27 associated disease. The most common sites of enthesitis are the calcaneal insertion of the Achilles tendon, plantar fascia and tarsal area. Arthritis commonly affects the joints of the lower extremities. Sacroiliac involvement and lumbosacral spine may occur.	3–11%	M>>F Early childhood or adolescence
Psoriatic arthritis Simultaneous presence of arthritis and a typical psoriatic rash or (if a rash is absent) the presence of arthritis and any two of the following: family history of psoriasis in a first-degree relative; dactylitis; and nail pitting	2–11%	F>M; biphasic distribution; early peak at 2–4 years and later peak at 9–11 years
Undifferentiated arthritis Includes children who do not satisfy inclusion criteria for any category, or who meet the criteria for more than one.	11–21%	

^a Reported frequencies refer to percentage of all juvenile idiopathic arthritis

in adults in several important aspects. Due to the peculiarities of the growing skeleton (the thickness of the articular cartilage varies among joints of children of different ages, ossification is incomplete, the presence of bone growth abnormalities etc.), the radiographic assessment of structural damage in JIA is challenging, and to apply adult-designed radiographic scoring systems to evaluate the progression of JIA may not be feasible.

In recent years there has been a great effort to devise paediatric-targeted radiographic scoring systems (Table 4); some of these measures have undergone a thorough validation process and have proved to be reliable and valid for assessment of radiographic progression in children with JIA. This has led to the suggestion that the time has come to include quantitative measure of radiographic damage in therapeutic trials in JIA, as recently proposed by Ravelli A [12].

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, such as inflammatory changes in the soft tissues, and drives the need for alternative imaging techniques that are more sensitive in detecting inflammatory processes, as well as the slightest traces of erosive joint damage. In this regard MRI and US are playing an increasing role in the evaluation of arthritic joints.

Advances in MRI

MRI provides multiplanar tomographic imaging with unprecedented soft-tissue contrast and allows assessment of all the joint structures involved in JIA (Table 5).

The knowledge of the pathological processes and clinical issues that have to be adequately imaged in JIA is essential for the choice of the variety of pulse sequences that are available for assessment of different joint components.

Table 3 Plain radiographic features in JIA

A. Soft-tissue swelling	
B. Osteopenia osteoporosis	
<ul style="list-style-type: none"> • Periarticular: due to the hyperaemia associated with joint inflammation • Generalized: due to decreased physical activity of the child, or the result of therapy e.g. steroids 	
C. Joint space narrowing	
D. Erosion	
E. Ankylosis	
F. Local growth disturbances:	
<ul style="list-style-type: none"> • Advanced skeletal maturation and epiphyseal enlargement are secondary to inflammation-induced chronic hyperaemia and growth factor release • Shortening is the result of early fusion of the cartilaginous growth plate • Focal skeletal modelling abnormalities are the result of irregular traction on growing structures, that are secondary to muscle spasm and periarticular fibrosis 	
G. Periostitis: particularly frequent along the shafts of the proximal phalanges, metacarpals, and metatarsals	
H. Abnormal joint alignment (i.e. joint subluxation, dislocation and flexion/extension defects)	
I. Calcification: intra-articular, capsular or periarticular calcifications may be seen following a single or multiple steroid joint injections	
Advantages	Disadvantages
1. Low cost	1. Use of ionizing radiation
2. High availability	2. Not sensitive in detecting inflamed and enhanced synovium, fibrocartilaginous structures or bone-marrow changes
3. Helpful in differential diagnosis	3. Limited and non specific for diagnosis of early JIA changes at diagnosis
4. Reproducibility	4. Reveals late and often irreversible structural damage
5. Validated assessment methods	5. Projectional superimposition
	6. Unable to directly detect cartilage changes or damage

A, B early but no specific finding; *C, D, E, H* late and often irreversible findings; *F* unique to arthritis in growing skeleton development

Choosing the best protocol for a specific indication is crucial in order to maximize cost-effectiveness and optimize diagnostic information of MRI.

In the last decade there has been a great deal of effort by the OMERACT (outcome measures in rheumatology clinical trials) MRI-RA group aiming to quantify the large amount of information produced by MRI, and culminating in the development and validation of a semi-quantitative scoring system for the assessment of inflammatory and damage abnormalities in RA. Consensus MRI definitions of important joint pathologies and a core set of basic MRI sequences were also suggested [13]. Despite the large number of studies available in adults, the experience on the use of MRI in the assessment of JIA is limited. So far pilot MRI grading scores for the assessment of hip and knee disease activity and damage of JIA patients have been proposed [14–16]. However, these scales have not been validated and have been tested on a limited number of patients. The lack of validated MRI scales targeted to children and standardized MRI protocols, together with the heterogeneity in the quality of the methodology used, have strongly affected the results of a recent systematic review of the literature, according to which the quality of reporting of methods in studies on the MRI assessment of JIA is heterogeneous and fair overall [17, 18]. Furthermore, as

outlined by the authors, long-term studies on MRI are lacking, therefore it is difficult to make treatment recommendations on MRI findings alone, as the long-term significance of these abnormalities is still unclear.

Notwithstanding and being aware of these limitations, we report below the more recent advances in MRI assessment of pathological findings in JIA and the way how they have changed our view of the disease.

Advances in MR imaging of synovial inflammation

MRI is the most sensitive imaging modality available for the detection of ongoing synovial inflammation, the primary target abnormality in JIA. Contrast-enhanced MRI allows a reliable differentiation of pannus from joint effusion (Figs. 1 and 2), an accurate differentiation of the active destructive hypervascular pannus from the inactive fibrotic pannus, and is able to show persistent synovitis in subclinical patients [14, 19, 20]. Of note in children with oligoarticular JIA, imaging of clinically unaffected joints has suggested that subclinical MRI-observed features of arthritis may predict extension of arthritis [21].

As the goal of new treatment is to obtain total suppression of joint inflammation to prevent erosive

Table 4 Radiographic scoring methods developed to measure radiographic damage in JIA

Study	Scoring methods	<i>n</i>	Type of joints
Pettersson et al. [79]	Knee score	15	Knee
Poznanski et al. [80] and Magni-Manzoni et al. [81]	Poznanski score	94	Wrist
Doria et al. [82]	Conventional and the modified Larsen’s system	60	Wrists/hands
Van Rossum et al. [83]	Dijkstra composite score	66	Hand, foot, and knee
Rossi et al. [84]	Sharp and Larsen scoring systems	25	Wrist/hand
Ravelli et al. [85]	Adapted version of the Sharp/van der Heijde score	177	Wrist/hand
Bertamino et al. [86]	Childhood arthritis radiographic score of the hip	148	Hip

damage, future outcome measures in both clinical trials and clinical practice, should comprise sensitive and robust measures of inflammation. Computerized measurements of synovial volumes (Fig. 3) have been found to be useful for the evaluation of disease activity and responsiveness to

treatment, as well as in predicting progressive joint destruction in RA [22–26]. In line with the results of studies in RA, Graham et al. [27] demonstrated the feasibility of MRI synovial volume measurement as an objective, quantitative method to assess disease activity in

Table 5 MRI features in JIA

- Joint effusion: low signal on T1-W and high signal on T2-W images.
- Synovitis: an area in the synovial compartment that shows increased contrast medium enhancement of a thickness greater than the width of the normal synovium.
- Bone marrow oedema: a lesion within the trabecular bone, with ill-defined margins and signal characteristics consistent with increased water content. May occur alone or surrounding an erosion or other bone abnormalities.
- Bone erosion: erosions typically show well-defined, rounded margins and may contain synovial fluid or synovial tissue and must be visible in two planes.
- Signs of cartilage damage: cartilage thinning, erosions, and deep cartilage loss manifest as areas of abnormal low signal intensity on proton density or T2-W sequences.
- Tenosynovitis: effusion and pathological enhancement of the synovial sheath.
- Enthesitis: inflammation of a tendon insertion site. It is common in enthesitis-related arthritis. Enthesitis can cause periosteal changes in the bone.

Advantages

1. Lack of ionizing radiation
2. Marked soft-tissue contrast
3. Multiplanar tomographic imaging
4. Early detection of erosive changes
5. Soft-tissue inflammation detection
6. Direct visualization of cartilage
7. Bone marrow oedema visualization

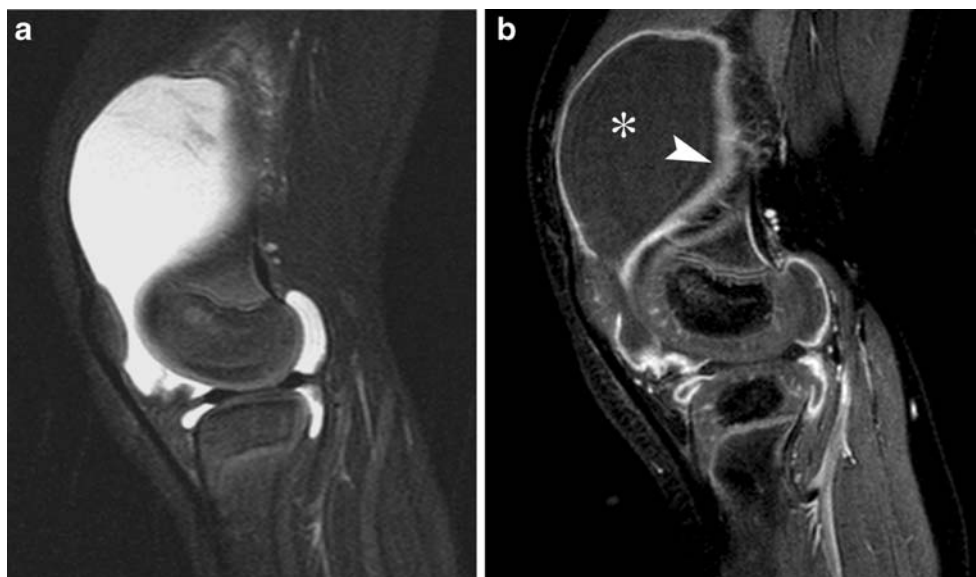
Disadvantages

1. High cost
2. Longer examination time
3. Sedation or general anaesthesia required in the younger or uncooperative child.
4. Potential allergic contrast reaction
5. Evaluation limited to one target joint
6. Availability varies worldwide

Clinical applications

- Assisting in the initial diagnosis and in the differential diagnosis process
- Assessing disease activity in clinically difficult joints such as the hip, sacroiliac joints, temporo-mandibular joint and the subtalar joint [87, 88]
- Helpful in identifying children who are most likely to develop joint damage from those who will have a mild disease course [19]
- Helpful in selecting children for treatment and to monitor treatment efficacy [19]
- Detecting subclinical synovitis [20]
- No data are available on the predictive value of soft-tissue changes with regard to future cartilage degeneration and functional status of the joints
- The role of MRI measurements in routine clinical care for defining remission, determining optimal treatment and predicting long-term response to therapy remains to be established

Fig. 1 Sagittal MR images of the knee in a 5-year-old girl with JIA. The fat suppressed (FS) T2-weighted fast spin-echo (FSE) sequence (a) and the contrast-enhanced FS T1-weighted sequence (b) show a large rim-enhancing joint effusion with thickened synovial margins, compatible with synovitis. The gadolinium-enhanced T1-W sequence (b) better differentiates fluid (*) and synovium (arrowhead). The radially arrayed enhancement of the articular cartilage of the distal femur epiphysis following gadolinium administration represents prominent penetrating vessels



children with JIA. Synovial volume, obtained using a semi-automated segmentation program from the hands and wrists, correlated well with local clinical signs of inflammation and with the total number of active joints, arguing for the utility of the wrist as a surrogate marker for total burden of synovitis in JIA. Of note Gylys-Morin et al. [28] showed that synovial volume had greater sensitivity (97%) than maximal synovial thickness (77%) in distinguishing clinical synovitis. Finally it has been shown that a decrease in pannus volume and enhancement in the hips and knees of JIA patients, correlated well with favourable clinical outcome [19]. In addition to volume measurement, 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. DCE-MRI has been shown to be a

sensitive and accurate method for estimating synovitis monitoring response to therapy, as well as for predicting future bone damage in patients with RA [29–34].

In accordance with the studies performed in adults, Malattia et al. [35] recently demonstrated that DCE-MRI is a reliable and accurate tool for quantifying the degree of synovial inflammation in JIA, especially in patients with wrist arthritis.

Workie et al. [36] have proposed the use pharmacokinetic modelling to quantitatively analyze dynamic synovial enhancement of the knee of children with JIA. Quantification of DCE-MRI data, by means of pharmacokinetic models, aims to calculate absolute measures that are directly related to tissue physiology such as vessel permeability. These absolute measures lend themselves well to longitudinal studies, as confirmed by the same authors in a subsequent study, in which it was shown that quantitative DCE-MRI (based on pharmacokinetic modelling) may be used as an objective follow-up measure of therapeutic efficacy in JIA; of note in the same study,

Fig. 2 MR images of both hips in children with JIA. a Coronal FS T1-W contrast-enhanced sequence in a 14-year-old girl shows bilateral synovitis with synovial contrast enhancement. b Coronal TSE T1-W image in another girl shows bilateral extensive erosive changes (arrows) on the femoral epiphyses

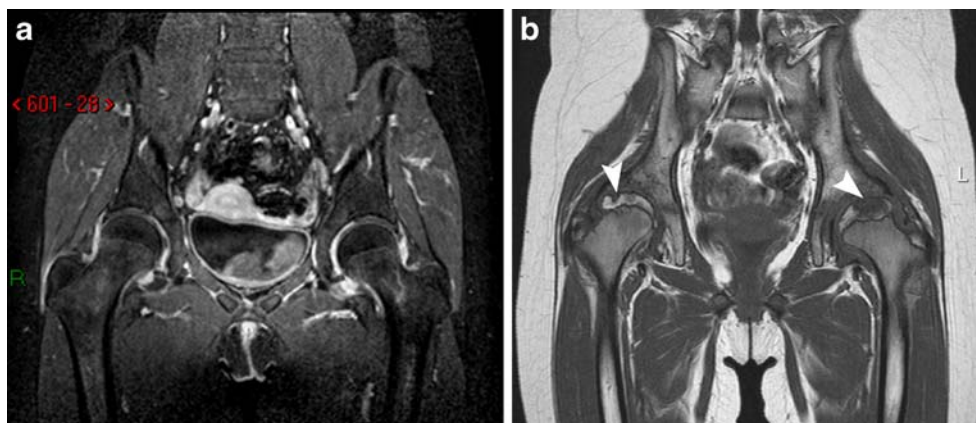
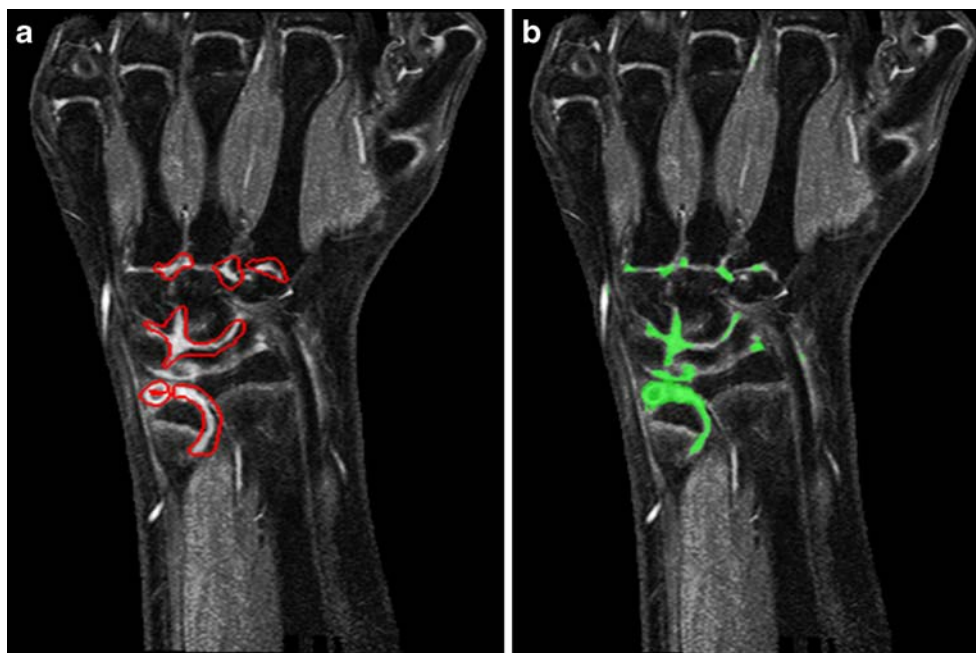


Fig. 3 Coronal FS gradient-echo (GRE) contrast-enhanced 3-D T1-W sequence of a wrist in a child with JIA. The results of synovial segmentation process for the evaluation of total volume are reported in a single coronal slice, as an example. Computerized measurements of synovial volume may be obtained either by manual (*red selection*) computer-assisted outlining base on visual analysis of the images (a) or by semiautomatic (*green selection*) computerizing counting of pixels fulfilling specific criteria (b)



improvement in synovial volume appeared to lag behind dynamic parameters [37].

The use of fully automated voxel-by-voxel analysis of signal intensity versus time curves, extracted from MRI dynamic slices, has been recently demonstrated to overcome the shortcomings of the region-of-interest (ROI) approach (sampling error and inter-user variability) and provide a truly objective overview of the tissue behaviour in the whole imaged area in patients with RA [38]. Through the use of a computer-assisted detection (CAD) programs, dynamic parameters are estimating for each voxel and presented in a form of parametric colour maps, providing an advanced visual aid for assessment of the spread and magnitude of the inflammation in the affected joint.

How has MRI changed our view of JIA?

- Synovitis is the primary target of the disease
- Synovitis is coupled with damage
- Patients in clinical remission may have persistent synovitis

Advances in MR imaging of bone marrow oedema

MRI is the only technique able to visualize bone marrow oedema (BME) (Fig. 4), one of the most intriguing MRI features in inflammatory chronic arthritis. Longitudinal studies, in fact, have demonstrated that BME is a key predictor of erosive joint damage in patients with RA [39, 40]. Recent studies of bone histology from joint replacement specimens in RA revealed that regions of MRI BME contain an inflammatory cellular infiltrate that is in close apposition

to activated osteoclasts, implying cross-talk and a possible mechanism to explain the development of erosions [41]. The prognostic value of BME in JIA has not yet been established, even though significant work in the adult field suggests that exploration of this area would be fruitful.

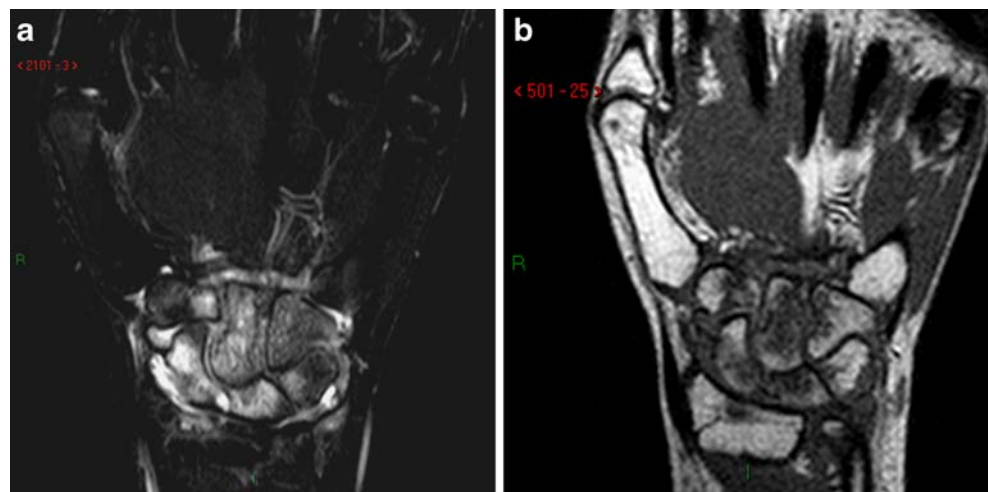
How has MRI changed our view of JIA?

- Bone erosions and BME are intimately linked from the pathophysiological perspective
- If the prognostic value of BME would be demonstrated even in JIA, BME should be regarded as a red flag for treating physicians and active management with powerful anti-erosive medications should be considered

Advances in MR imaging of cartilage

Another unique strength of MRI is its ability to directly visualize articular cartilage. Direct imaging of this tissue is more specific than radiographic joint space width and tomography provides greater anatomical coverage of the joint surface than does projection. With the use of dedicated sequences it is possible to accurately assess signs of cartilaginous damage, such as thinning, erosions and deep cartilage loss in JIA patients, and to discriminate different types of cartilage (articular, epiphyseal, and physeal) at distinct stages of development of growing joints (Fig. 5) [19, 42, 43]. The administration of contrast medium was found to be useful for the characterization of cartilage thickness and erosions as well as the pattern of enhancement (peculiar, striated, or linear) of the cartilaginous epiphyses in JIA patients [16, 44, 45]. Newer pulse

Fig. 4 13-year-old girl with JIA. Coronal FS T2-weighted fast spin echo (FSE) sequence (a) and coronal T1-weighted TSE sequences (b) of the wrist. Presence of diffuse bone marrow hyperintensity in FS T2-w (a) and hypointensity in T1-w (b) sequences respectively, consistent with bone marrow edema



sequences such as ultra-short TE sequences, driven equilibrium Fourier transform (DEFT) imaging, and steady-state free precession (SSFP) sequences appear promising in the detection of subtle surface irregularities and tiny focal defects of the articular cartilage [46–49]. In addition, sophisticated analysis of 3-D image data can provide articular surface contour mapping, 3-D rendering and volumetric quantification of articular cartilage that can be used to evaluate the progression and response to treatment in patients with chronic arthritis. This technique may be useful for monitoring changes in cartilage volume over time in JIA patients. However further studies are needed in this field in the

paediatric population, and measurements correlating normal articular cartilage volume with age have to be developed.

Of particular interest Kight AC et al. [50] recently suggested the role of T2 relaxation time properties in measuring the mobility of cartilage water that is sensitive to the integrity of collagen in the extracellular matrix. The finding of an increased average T2 relaxation time of the distal femoral weight-bearing cartilage in patients with JIA, compared with sex- and age-matched healthy control subjects, suggests that T2 relaxation time maps may reflect cartilage microstructure differences that occur in JIA. Correlations between the transverse relaxation rate and collagen concentrations in the cartilage matrix have been previously demonstrated in a study in engineered cartilage tissue [51]. These specialized T2-mapping sequences, allowing an assessment of the biochemical and biophysical changes in the extracellular cartilage, and providing information about very early cartilage damage (before morphologic changes can be qualitatively detected with conventional imaging methods), represent a powerful method of monitoring disease progression with the long-term potential to guide therapy.

Furthermore, once translational studies on new functional MRI techniques are performed, new insights into the biological pathways of cartilage turnover will improve our understanding of the physiopathogenesis of JIA.

How has MRI changed our view of JIA?

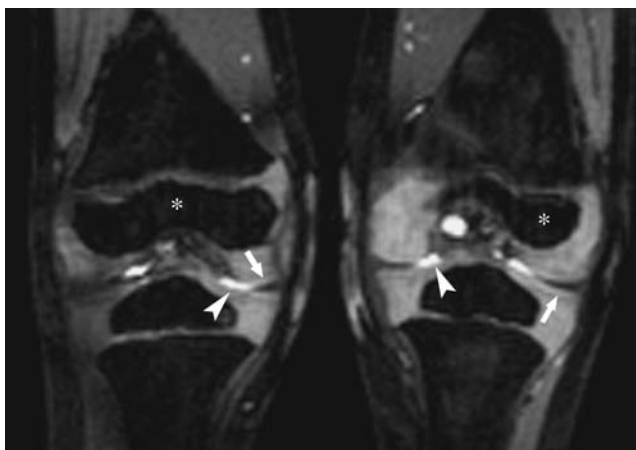


Fig. 5 Coronal image of the knee in a healthy 5-year-old boy obtained with a balanced turbo field echo (BTFE) FS sequence for cartilage evaluation. In addition to high image SNR, cartilage imaging demands contrast between cartilage and structures such as synovial fluid and bone. In this example at the distal end of the femur the central ossified epiphysis (*) is of low signal intensity. The epiphysis is surrounded by high-to-intermediate signal intensity growth cartilage. Along the joint margins the articular cartilage is of slightly high signal intensity and can be differentiated from growth cartilage (arrows). Note the good contrast between articular cartilage (arrows) and synovial fluid (arrowheads)

- Quantitative imaging may potentially provide information beyond morphological changes in articular cartilage, with regard to early cartilage damage
- Cartilage matrix changes can be detected at stages when damage to the cartilage is still reversible and may be treated
- Research in the field of composition of the cartilage matrix is driven by the technological developments and may provide pathophysiologic information relevant to disease progression

Advances in MR imaging of bone erosion

Early detection of bone erosions and subchondral changes, and aggressive control of the disease is of outstanding value in decreasing the chance of further disability. Consistent with the results of previous studies in RA patients Malattia C et al. [52] in a pilot multi-imaging study, demonstrated that MRI was the most sensitive imaging modality for detection of bone erosions in the wrist of patients with JIA, revealing more than twice as many erosions as radiography and US [53–57]. The increased accuracy of MRI in detecting erosive changes was much more evident in the group of patients with shorter disease duration. All patients with shortstanding disease showed minor erosive changes revealed by MRI. An early concern that increased sensitivity of MRI may be at the cost of reduced specificity and that MRI erosions were “not real” has now largely been debunked by comparison with the 3-D radiographic technique of CT scanning [58, 59].

Studies on adults with RA have demonstrated the significant prognostic value of MRI detectable structural damage with respect to long-term radiographic erosive damage [57, 60]. The greater sensitivity of MRI to disclose incipient destructive changes could be leveraged to select patients for more aggressive therapy and to monitor treatment response. Predicting prognosis in children with newly diagnosed JIA is of key importance in order to tailor treatment to the risk of disability. However, before using MRI in guiding therapeutic decision, further longitudinal studies are needed to determine the real prognostic value of MRI detectable bone lesions.

Less work has been done looking at computerized measurements of erosion volume on MRI compared with synovial volume; this most likely reflects the difficulties in estimating the proximal bone outline prior to erosion [24]. Computerized software advances should improve automation of the segmentation process.

How has MRI changed our view of JIA?

- Bone erosion is common in the early course of the disease
- MRI could be helpful to identify patients at increased risk of developing erosive disease and who will benefit from more aggressive treatment at an early stage

Advances in US

The use of US and colour Doppler continues to increase as resolution of the equipment improves; in fact the visualization of any intra-articular structures is significantly improved by the use of high frequency (12–18 MHz) linear probes.

The severity of joint involvement may be judged sonographically by parameters such as the size of the

effusion, synovial thickening, cartilage thinning and bone erosions. Colour and power Doppler facilitate detection of hyperaemia and vascular abnormalities (Table 6) [61]. US can also be used to assess tenosynovitis and to guide joint aspiration or injection.

However, the major limit of US (joint accessibility) limits its applicability in “difficult joints” such as the temporo-mandibular joint (TMJ), sacroiliac joints etc. In a recent report, Muller et al. [62] concluded that US is not able to reliably exclude active TMJ arthritis and that MRI of the TMJs should be performed in children with JIA.

Synovial thickening and effusion

Sonography is more sensitive than plain radiography or clinical examination in the detection of effusion, synovial thickening and synovial cysts [16, 19]. Recent studies in children with JIA have shown that clinical examination may underestimate significant joint inflammation when compared with US, especially in the small joints of the hands and feet [63, 64]. Furthermore inflammatory involvement of the hip, shoulder and elbow is more frequently accurately detected by US compared with clinical examination (Fig. 6).

The issue of US detectable subclinical synovitis may be particularly relevant in JIA. In the current ILAR classification, children with JIA are defined as having oligoarthritis or polyarthritis on the basis of the number of affected joints. The presence of active disease in a minimum of five joints is necessary for the diagnosis of polyarticular JIA, as well as being a prerequisite for patient inclusion in clinical trials of second-line or biologic agents [6, 65, 66]. Identification of subclinical disease may change patient classification and potentially alert the treating physicians towards more aggressive treatment and close monitoring of the patient.

It is well established that serial US may supplement clinical assessment in monitoring disease activity and in evaluating response to therapy, especially in hip synovitis. Eich et al. [45] in fact, demonstrated that US is a useful tool to assess effusion and pannus after intra-articular steroid injection in a cohort of JIA patients with hip and knee active arthritis. In this regard, colour Doppler provides an indication of the degree of synovial hypertrophy and assessment of its vascularity may be particularly useful (Fig. 6). In addition, resistive indices and fraction of colour pixels have been proposed as quantitative measurements of blood flow [67, 68].

Strunk J et al. [69] in a recent study compared 3-D power Doppler US (3-D PDUS) with contrast-enhanced MRI in their ability to visualize synovial vascularity in inflamed wrists of patients with RA. The analyses of the obtained 3-D images allowed differentiation between intra- and extra-articular blood vessels, as well as quantification of intra-articular blood vessels in a well-defined ROI,

Table 6 Musculoskeletal US findings including definitions for US pathology according to OMERACT seven special interest group

US findings in JIA

- Joint effusion: abnormal hypoechoic or anechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intra-articular material that is displaceable and compressible, but does not exhibit Doppler signal
- Thickening of synovial membrane: abnormal hypoechoic (relative to subdermal fat, but may be isoechoic or hyperechoic) intra-articular tissue that is non displaceable and poorly compressible and may exhibit Doppler signal
- Hypertrophic bursopathy: hypoechoic irregular thickening of the synovial membrane surrounding effusion of a bursa (i.e. subacromial-subdeltoid bursa)
- Tenosynovitis: hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath that is seen in two perpendicular planes and which may exhibit Doppler signal
- Cartilage thinning and erosions: alteration in the contour seen as blurring and obliteration of the normally sharp margins of the cartilage surface
- Bone erosions: an intra-articular discontinuity of the bone surface that is visible in two perpendicular planes

Advantages

1. Lack of ionizing radiation
2. Non-invasive, well tolerated
3. Relatively low cost
4. Repeatability
5. Possibility of examining several joint regions at one session
6. Ability to visualize both inflammatory and destructive disease manifestations
7. Potential for guiding interventions (i.e. intra-articular steroid injection)

Disadvantages

1. Operator dependence
2. Not all joints accessible, the whole joint space not assessed
3. Reduced joint movement in case of joint tenderness and pain
4. Small field of view
5. Acoustic shadowing from overlying bones
6. Difficult to standardize and centralize for clinical trials

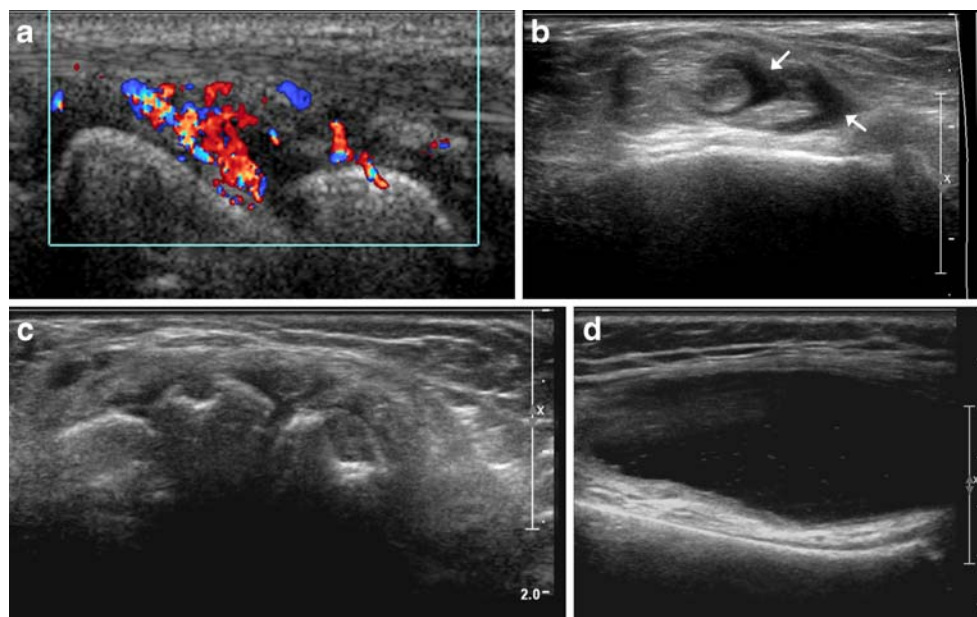


Fig. 6 **a** Longitudinal US scan over the dorsal aspect of the wrist shows abnormal hypoechoic synovial tissue at the level of the dorsal recess of the intercarpal joint. Colour Doppler gives an indication of the degree of synovial vascularity. **b** US scan of the peroneal tendons obtained transversely to their long axis at the lateral aspect of the ankle shows hypoechoic thickened tissue (*arrows*) within the tendon

sheath that is indicative of mild tenosynovitis. **c** Transverse scan over the dorsal aspect of the wrist in a child with JIA shows evidence of a focal discontinuity of the bone surface of the capitate (it is considered an erosion if it is confirmed in two perpendicular planes). **d** Longitudinal scan of the suprapatellar recess of the knee shows presence of effusion and synovial hypertrophy

providing a new approach for numerical quantification of synovial vascularisation.

The administration of US contrast agent has been shown to further improve the detection and assessment of the vascularity, thanks to the recent availability of real-time contrast-enhanced US imaging and software for quantification of data. The value of this technique in improving diagnosis, staging activity of the disease and monitoring therapy efficacy has been demonstrated in patients with RA [70].

Cartilage thinning and erosions

US allows direct visualization of articular cartilage that is normally seen as a hypoechoic structure with a smooth outline over the bone surfaces. The reliability of the assessment of cartilage thickness with US has been recently demonstrated by Spannow et al. [71] in a cohort of healthy children of different ages. The authors found a good intra- and interobserver agreement both in large and small joints, using ultrasonographic standard scans according to EULAR guidelines. Furthermore Moller et al. [72] have recently demonstrated that the US method of direct visualization and quantification of cartilage in metacarpophalangeal and proximal interphalangeal joints is objective, reliable and valid, and suggested its use for diagnostic purposes in patients with RA. However, further studies aiming to collect more data on the expected normal cartilage thickness in children of different ages are needed in order to provide an accurate assessment of cartilage thinning in JIA.

In line with previous studies in RA, recent studies on JIA confirmed that US is equal or superior to CR in detecting cortical erosions in sonographically accessible areas (Fig. 6), but it is less reliable in detecting intramedullary lesions and those within the centres of larger joints, due to the acoustic shadowing from overlying bones [52, 73, 74].

Tenosynovitis

It is well established that US is sensitive in the detection of the full spectrum of tendon pathology (Fig. 5). In a recent paper Rooney et al. [75] demonstrated the extremely useful role of US in the evaluation of the anatomical basis for clinically detected ankle joint swelling in JIA. Physical examination is, in fact, very difficult in younger children due to the distribution of fat, the lack of prominent anatomical landmarks and poor co-operation, making the distinction between joint synovitis and tenosynovitis difficult. Their findings showed an unexpectedly high degree of tenosynovitis, which was often the only abnormality. This could be important for the diagnosis and therapy of JIA and potentially for classification purposes. In fact, in their conclusions the

authors postulate that a substantial number of children may be wrongly classified as having extended oligoarticular or polyarticular disease on the basis of ankle involvement, when they have oligoarticular disease with tenosynovitis. Their findings however, as recently mentioned by McGonagle and Benjamin [76], have also potential implications for a new clinico-immunopathological classification of JIA; the authors argue that US findings could provide a platform for a better anatomical US-based classification of JIA.

In conclusion, US may be a valid method for monitoring synovitis and, in accessible areas, erosive progression, even if more data on reproducibility and sensitivity to change are needed. Furthermore the assessment of joints with US is still limited by the fact that US cannot penetrate bone, by intermachine and inter-reader variability, by lack of consensus on systems for assessment of activity and damage, and by limited testing of the available systems in longitudinal follow-up studies.

How has US changed our view of JIA?

- US is sensitive in detecting subclinical synovitis
- US has a potential role in improving JIA classification
- US is sensitive for assessment of disease activity and damage
- Expanding role of US in monitoring treatment efficacy should be encouraged

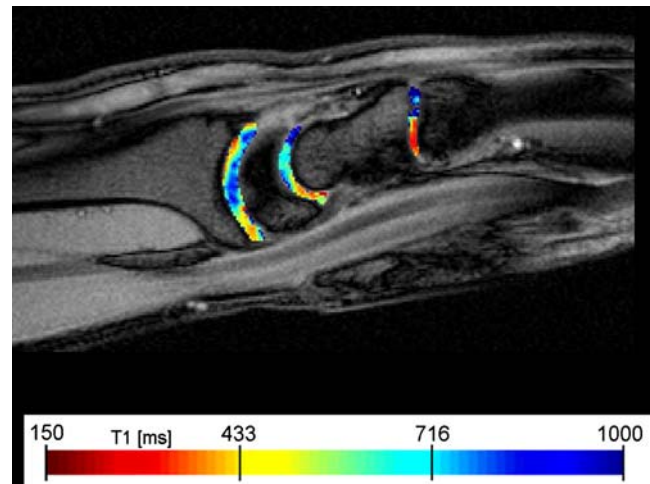


Fig. 7 T1 mapping as a result of delayed gadolinium enhanced imaging of cartilage (dGEMRIC) for the evaluation of articular cartilage in a mid sagittal plane of a wrist in a patient with JIA: radio-lunate, luno-capitate and capitate-3rd metacarpal base joints. dGEMRIC is a technique that specifically looks at glycosaminoglycans (GAGs). $\text{Gd}(\text{DTPA})^{2-}$ can be used to evaluate the fixed charge density of the cartilage which is closely related to the GAG concentration. T1 map reflects the concentration of $\text{Gd}(\text{DTPA})^{2-}$ in the cartilage. GAGs are negatively charged and they repel ionic gadolinium. When there is a breakdown of GAGs, cartilage loses its negative charge and allows more $\text{Gd}(\text{DTPA})^{2-}$ into its matrix with a shorter T1 relaxation time, on the contrary areas with GAG integrity have a lower concentration of gadolinium, and therefore have longer T1

Future prospective in imaging in JIA

New imaging techniques are under evaluation for better and earlier assessment of synovial, cartilaginous or osseous abnormalities. It is, however, in the field of MRI that the most exciting advances are expected with the implementation of diffusion-weighted and perfusion imaging techniques, delayed gadolinium-enhanced cartilage imaging, T2 relaxation time mapping and quantitative computer-assisted tools for MRI analysis. Diffusion-weighted imaging (DWI), by detecting microscopic changes in water mobility, allows an indirect assessment of tissue integrity. This technique is promising for evaluating very early cartilage abnormalities by detecting collagen fibre degradation [77].

Dynamic contrast-enhanced MRI may allow detection of the perfusion imaging of each anatomical compartment of the joint and direct therapeutic scheduling according to enhancement patterns.

Delayed gadolinium-enhanced MR cartilage imaging (dGEMRIC) is a sensitive technique for assessing cartilage proteoglycan content, using the negative charge of the paramagnetic MR contrast agent (Fig. 7). The contrast agent distributes into the cartilage inversely to the fixed charge density of negatively charged glycosaminoglycans (GAG) [77]. Thus, T1 relaxation time, in presence of this contrast agent, is approximately linearly related to the glycosaminoglycan content. dGEMRIC may be used to assess early cartilage injury that occurs before morphologic cartilage damage can be detected by conventional imaging.

The recent development of 3-T MRI, with its increased signal-to-noise ratio (SNR), gives us the opportunity to obtain clearer images, better resolution and faster scans. Cartilage can be clearly visualized and pathology more easily detected due to increased image quality [78]. To date, both animal and human imaging has also been performed on a whole-body 7-T scanner, with promising results in terms of detailed imaging and functional data. However the road ahead is long and we cannot predict the end of this exciting adventure with higher field strengths.

Conclusion

With the availability of new exciting imaging tools a wide range of morphological, functional and biochemical data will be available. Translational studies will further improve our understanding of the pathogenesis of the disease through the integration of radiological findings with clinical, genetic and immunological data. In this context it is crucial that the radiologist and paediatric rheumatologist work in a multidisciplinary team including experts in bio-imaging processing and analysis as a more extensive use of imaging will also depend on computer-assisted diagnostics.

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