Magnetic resonance imaging in juvenile idiopathic arthritis diagnosis and follow-up, beyond imagination
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Chapter 1

General introduction

This chapter is adapted from:
Hemke R, Maas M. MRI of the knee in juvenile idiopathic arthritis
Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is the most common auto-inflammatory musculoskeletal disease in childhood. Its yearly incidence in developed countries varies from 2–20 cases per 100,000 and its prevalence from 16-150 cases per 100,000 (1). JIA is no solitary entity. The term encompasses all forms of arthritis that start before the age of 16 years, persist for more than 6 weeks, and are of unknown etiology and pathophysiology (2). The term JIA includes 7 well defined disease categories, marked by distinct presentations, clinical features, and in some cases genetic backgrounds.

Subgroups of JIA have been described by Petty et al. (2) as follows:

- **Oligoarthritis.** Oligoarthritis is characterized by asymmetric arthritis, early onset (<6 years of age), high female-to-male ratio, high concentration of positive antinuclear antibodies (ANA) and a high risk of developing iridocyclitis. Two subcategories are recognized: persistent oligoarthritis, and extended oligoarthritis. Persistent oligoarticular JIA is defined by the international league of associations for rheumatology (ILAR) as an arthritis that is confined to four or fewer joints. Children who otherwise satisfy these criteria are excluded from the oligoarthritis category if they have psoriasis, a family history of psoriasis, a human leukocyte antigen B27-associated disease in a first-degree relative, a positive rheumatoid factor test, or if the disease occurs in a male patient older than 6 years (2). The extended oligoarthritis subtype in JIA is defined as an arthritis that affects four or fewer joints but extends to more than four joints after the first six months of the disease (2). Involvement of an upper limb joint and high erythrocyte sedimentation rate (ESR) at onset have been identified as predictors for an evolution from the persistent subtype to the extended phenotype, which occurs in up to 50% of patients (3, 4).

- **Rheumatoid factor (RF) positive polyarthritis.** RF-positive polyarthritis is defined as an arthritis that affects five or more joints during the first six months of the disease, and which includes the presence of an IgM RF on at least two occasions more than three months apart (2). This subtype of JIA has a similarity to adult RF-positive rheumatoid arthritis (RA). A typical presentation is a symmetric polyarthritis in adolescent girls that affects the small joints of the hands and feet, however large joints such as the knee and ankle are frequently involved as well.

- **Rheumatoid factor (RF) negative polyarthritis.** RF-negative polyarthritis is defined as an arthritis that affects five or more joints during the first 6 months of disease in the absence of IgM RF (2). This subtype of JIA is probably the most heterogeneous.
• **Enthesitis related arthritis (ERA).** Enthesitis related arthritis mainly affects male patients after the age of six years. It is defined as an arthritis and enthesitis, or arthritis or enthesitis with at least two of the following: 1. the presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbo-sacral pain, 2. the presence of HLA-B27 antigen, 3. onset of arthritis in a male over six years, 4. acute (symptomatic) anterior uveitis, and 5. a history of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative (2). This form of arthritis commonly affects the joints of the lower extremities.

• **Psoriatic arthritis.** Psoriatic arthritis is by ILAR defined as an arthritis combined with psoriasis, or an arthritis and at least two of the following: dactylitis, nail pitting or onycholysis, and psoriasis in a first-degree relative (2). The association of psoriasis with arthritis seems to lead to the identification of two subsets of patients, one with disease that is similar to adult psoriatic arthritis and another with disease that has only minor differences with ANA-positive oligoarthritis (5).

• **Systemic arthritis.** Systemic arthritis differs from other subtypes. The disease arises as often in boys as in girls and does not show a preferential age of onset. It is defined as arthritis in one or more joints with or preceded by fever of at least two weeks duration that is documented to be daily for at least three days. Thereby it should be accompanied by one or more of the following: evanescent (nonfixed) erythematous rash, generalized lymph node enlargement, hepatomegaly and/or splenomegaly, and serositis (2). Onset in adults, known as Still's disease, is rare. Laboratory investigations show leukocytosis (with neutrophilia), very high ESR and C-reactive protein concentration, and thrombocytosis.

• **Undifferentiated arthritis.** This subtype of JIA includes patients who do not satisfy inclusion criteria for any category, or who meet the criteria for more than one (2).

The clinical symptoms include swollen joints as well as joints with tenderness or pain on motion and a limited range of motion. As shown in Chapter 2, the knee is – upon clinical assessment – the most commonly affected joint in JIA both at the first visit and during a follow-up period of 5 years, followed by the ankle, elbow and wrist. In JIA, synovial proliferation and infiltration by inflammatory cells occurs in affected joints, resulting in increased secretion of synovial fluid and synovial hypertrophy. Persistent synovitis may culminate in articular cartilage lesions and bone erosions, which cause disability and reduced quality of life in JIA (6-9). As early therapeutic intervention with highly effective anti-rheumatic medication improves long-term outcome (10, 11), accurate measures in the assessment of disease activity, individual response to therapy, efficacy of treatment and long-term outcomes in JIA are essential.

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Imaging

Three imaging modalities are currently available for the evaluation of disease status in pediatric JIA patients. These are conventional radiography, ultrasonography and magnetic resonance imaging (MRI). Radiological evaluation of children's joints is challenging. Skeletal growth and maturation in children are dynamic processes. Therefore it may be difficult to establish whether differences in the appearance of a joint are pathological or a part of normal maturation.

Conventional radiography

Up to the present day, conventional radiography still is the most commonly used imaging modality for the assessment of disease status in JIA. It is the traditional standard for the evaluation of joint damage, including bone erosions, narrowing of the joint space, joint subluxation, misalignment, and ankylosis. Preventing or limiting joint destruction is the major goal of treatment in JIA. However, no guidelines are available and controlled trials - even those concerning new agents such as TNF-α blockers - do not include assessments of radiographic progression. An overview of the advantages and disadvantages of CR is provided in Table 1.

Table 1. Advantages and disadvantages of conventional radiography in juvenile idiopathic arthritis

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Conventional radiography</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>1. Low cost</td>
<td>1. Not sensitive in detecting soft tissue abnormalities as well as early erosive changes</td>
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<tr>
<td>2. High availability</td>
<td>2. Limited and non specific for diagnosis of early JIA changes</td>
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<tr>
<td>3. Helpful in differential diagnosis</td>
<td>3. Use of ionizing radiation</td>
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<tr>
<td>4. Reproducibility</td>
<td>4. Reveals late and often irreversible structural damage</td>
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<tr>
<td>5. Validated assessment methods</td>
<td>5. Projectional superimposition</td>
<td></td>
</tr>
<tr>
<td>6. Unable to directly detect cartilage changes and damage</td>
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The evaluation of articular disorders in children differs from that in adults in several respects. One needs to be aware of the process of normal development in order to understand the growing joint. The growing skeleton develops throughout childhood. During the first few years of one's life, the majority of the epiphyses consist of non-ossified epiphyseal cartilage that cannot be distinguished from adjacent soft tissues by CR. With increasing age, epiphyseal cartilage is transformed into bone. This narrows the radiographic joint space to the thickness of the opposing layers of articular cartilage, as seen in adolescence or adulthood (Figure 1). This considerable cartilaginous component may hinder accurate depiction of damage or changes in cartilage on diagnostic radiographic investigation (12-14).
Figure 1. Growth. Conventional radiographs obtained in (from left to right) a 2-year old boy, a 6-year old girl, an 11-year old boy, and an 18-year old girl demonstrating narrowing of the radiographic joint space caused by the transformation of cartilage to bone.

Although conventional radiography provides important information in regard of growth disturbance and damage due to disease activity in JIA, early changes on CR are unclear whereas late changes may be permanent (15). For example, some early erosive changes can easily be detected by MRI, while unseen on conventional radiography (16). Thereby, modern therapeutic strategies have created a growing need for reliable imaging assessment tools, which should be standardized in order to evaluate the potential value of these drugs in preventing structural joint damage.

Early changes show inflammatory responses that coincide with synovial hypertrophy, such as soft tissue swelling, osteopenia, joint effusion, and periosteal reaction (17). However, the major disadvantage of CR is that it does not directly demonstrate synovial hypertrophy, which is one of the most critical hallmarks of disease activity in JIA. The focus on early suppression of inflammation to prevent cartilage lesions and bone erosions has shifted attention from damage identified on CR to the actual early manifestations of JIA, and emphasized the need for imaging techniques that are more sensitive for the evaluation of inflammatory processes and early erosive changes. In this regard, MRI and ultrasonography are playing an increasingly important role for the assessment of disease status and the follow-up of JIA patients.

**Ultrasonography**

The use of ultrasonography (US) is being used to an increasing extent for the evaluation of disease status in patients with JIA. Improvements in resolution have enhanced the performance of US. It is a safe, painless, and patient-friendly procedure without the use of ionizing radiation. US provides information on inflammatory as well as destructive changes of the joint. Table 2 summarizes the advantages and disadvantages of US.
US is more sensitive than conventional radiography or clinical examination for the detection of effusion, synovial hypertrophy, and bone erosions (18, 19). Some studies have shown that the clinical examination may underestimate significant joint inflammation when compared to US, especially with respect to the small joints of the hands and feet (20-22). Besides, US is able to depict subclinical synovitis in JIA patients who meet clinical criteria for remission, as some of these patients show ongoing pathologies on US (23). US images readily differentiate between joint effusion and synovial hypertrophy. The inflamed synovium appears as a thickened, rough, nodular hyper-echoic region covering the joint space. Normal cartilage is seen as a hypo-echoic structure with a smooth outline covering the outer surface of the bone, sometimes hard to discriminate from joint effusion (24). Despite the advantages of US in pediatric JIA patients, it lacks standardization and information on its reliability. Moreover the responsiveness of US to assess changes over time is unknown (25).

### Magnetic resonance imaging (MRI)

MRI is more sensitive in the assessment of inflammatory and destructive changes in JIA as compared to conventional radiography, ultrasonography, and physical examination (15, 26, 27). Within the past decade, the use of MRI and advances in MRI techniques has substantially improved evaluation of joint pathologies in JIA patients (28). MRI is the most sensitive imaging tool for the detection of synovial hypertrophy, the most critical hallmark of disease activity in JIA. It is also very sensitive for the detection of cartilage lesions and bone erosions (15). Furthermore, MRI is the state-of-the-art imaging modality able to visualize bone marrow changes, a potential predictor of early erosive joint damage. Therefore, despite practical limitations, MRI is considered

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**Table 2. Advantages and disadvantages of ultrasonography in juvenile idiopathic arthritis**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Ultrasonography</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>1. Lack of ionizing radiation</td>
<td>1. Operator dependence</td>
<td></td>
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<tr>
<td>2. Non-invasive / patient friendly</td>
<td>2. Not all joints accessible (e.g. knee)</td>
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<tr>
<td>3. Relatively low cost</td>
<td>3. Reduced joint movement in case of joint tenderness and pain</td>
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<tr>
<td>4. Possibility of examining several joint regions at one session (bilateral)</td>
<td>4. Small field of view</td>
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<tr>
<td>5. Ability to visualize both inflammatory and destructive changes</td>
<td>5. Acoustic shadowing from overlying bones</td>
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<tr>
<td>6. Potential for guiding interventions</td>
<td>6. Difficult to standardize and centralize for clinical trials</td>
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</table>
to be the most suitable imaging modality for the evaluation of disease status in JIA (28, 29). A summary of the advantages and disadvantages of MRI is provided in Table 3.

**Table 3.** Advantages and disadvantages of magnetic resonance imaging in juvenile idiopathic arthritis

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Magnetic resonance imaging</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lack of ionizing radiation</td>
<td>1. High cost</td>
<td></td>
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<tr>
<td>2. Marked soft-tissue contrast</td>
<td>2. Longer examination time</td>
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<tr>
<td>3. Multiplanar tomographic imaging</td>
<td>3. Sedation or general anesthesia may be required in younger children</td>
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<tr>
<td>4. Reproducibility</td>
<td>4. Potential allergic contrast reaction</td>
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<tr>
<td>5. Early detection of erosive changes</td>
<td>5. Availability varies worldwide</td>
<td></td>
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<tr>
<td>6. Detection of soft-tissue inflammation</td>
<td></td>
<td></td>
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<tr>
<td>7. Direct visualization of cartilage</td>
<td></td>
<td></td>
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<tr>
<td>8. Visualization of bone marrow edema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Ability to standardize for clinical trials</td>
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</table>

**Indication and MR imaging protocol**

Radiology plays an important role in the management of JIA. MRI is indicated in patients with suspected but not clinically detectable inflammation or synovitis, in patients with persistent pain and limited range of motion of unknown etiology, for exclusion of other musculoskeletal disorders, for monitoring response to therapy and disease progression, for the detection of complications, and for the evaluation of disease activity before terminating or altering therapy strategies.

The children are placed in supine position with the knee joint positioned centrally in the magnetic field using a dedicated knee coil. In Chapter 3 we evaluated the feasibility of bilateral non-contrast-enhanced open-bore MRI. It turned out that by using an open-bore MR system, unsedated scanning is feasible in JIA patients as young as 5 years of age. By using a dedicated knee coil adequate signal-to-noise ratio can be obtained. In Chapter 5 we assessed the diagnostic accuracy and reliability of MRI without contrast enhancement in the evaluation of JIA knee joint abnormalities. As omitting an intravenous gadolinium-containing contrast agent (Gd) leads to an increase in inter-reader variation and a decrease in agreement between contrast-enhanced and non-enhanced synovial hypertrophy scores, omitting Gd enhancement in MRI of joints in JIA is not recommended. Post contrast images should be obtained in the early phase (<5 min) after intravenous injection of Gd (0.1 mg per kilogram of body weight), because this permits optimal differentiation between enhancing synovium and joint effusion. As the synovial membrane has no tight junction or basement membrane, contrast agents will diffuse into the joint space and gradually increase the signal intensity of adjacent fluid (30).
MRI features for the evaluation of disease status in JIA

Synovial hypertrophy

The normal synovial membrane encompasses a small rim of tissue adjacent to the articular tissue. It produces synovial fluid, which lubricates and nourishes the cartilage and bone in the joint capsule. The synovium is composed of two layers; an intimal component of 1–3 discontinuous cell layers of synoviocytes (or synovial lining cells, which are fibroblasts and macrophages) with an incomplete basement membrane, and an outer subintimal layer which merges with the fibrous joint capsule and contains nerves, lymphatic’s and vasculature (31). The synovial lining covers fat pads and intra-articular ligaments such as the cruciate ligaments. Thus these structures are intra capsular but extra synovial (31). MRI is the most sensitive imaging modality for the evaluation of the synovial membrane. The physiological synovial membrane is of low signal intensity on both T1-weighted and T2-weighted images and is seen as a thin and smooth rim of tissue aligning the articular cartilage, which is no more than 2 mm thick (Figure 2).

Figure 2. Physiological synovial membrane. Sagittal T1-weighted images before (a) and after (b) the injection of Gd, and an axial T1-weighted fat saturated MR image (c) after the injection of Gd obtained in a 16-year old girl show a thin and smooth rim of tissue aligning the articular cartilage that is no more than 2 mm thick (arrows).

Synovial hypertrophy is the principle pathological process in JIA, although it may also be seen in diseases involving any other cause of arthritis, as well as periarticular tumors and conditions. However, the presence of synovial hypertrophy upon MRI is – as shown in Chapter 8 – significantly associated with the clinical onset of JIA. The inflamed synovial membrane is thickened, irregular and its outline may be wavy (Figure 3). The signal intensity of this hypertrophic synovial membrane is low to intermediate on T1-weighted images and high on T2-weighted images, similar to joint effusion. As shown in Chapter 5, the use of T1-weighted MR images before and after gadolinium facilitates better differentiation between joint effusion and synovial hypertrophy (Figure 2).
Figure 3. Inflamed synovial membrane. Sagittal T1-weighted images before (a) and after (b) the injection of Gd, and an axial T1-weighted fat saturated MR image (c) after the injection of Gd obtained in a 17-year old girl with clinically active JIA show a thickened, irregular synovial membrane with wavy outlines (arrows). Notice that injection of Gd facilitates better differentiation between joint effusion and synovial hypertrophy through better visualization of the hypervascularity of the synovial membrane.

Bone marrow edema

During the first year of life a bone marrow starts to be converted from the hematopoietic (red) to the fatty (yellow) type (32). This normal conversion in the appendicular skeleton nears completion at the time of skeletal maturity. However these changes occur throughout life in the axial skeleton. Bone marrow is transformed in accordance with a predictable pattern, from the periphery (phalanges of the fingers and toes) to the center (humeri and femora). The first process that occurs in every bone is epiphyseal conversion to fatty bone marrow within 6 months after the appearance of the secondary center of ossification on radiological investigation (33). The transformation from hematopoietic (high signal intensity on T2-weighted fat-saturated images and low on T1-weighted images) to fatty bone marrow (low signal intensity on T2-weighted fat-saturated images and high on T1-weighted images) continues in the diaphysis and proceeds towards the metaphyses (32). Consequently, the last parts to convert are the proximal humeral and femoral metaphyses (34-36). Therefore, hematopoietic marrow can be seen into early adulthood in these locations.

MRI is the state-of-the-art imaging technique to visualize changes in bone marrow suggestive of bone marrow edema. The latter is seen as lesions within trabecular bone, with poorly defined margins. Bone marrow edema is marked by high signal intensity on T2-weighted fat-saturated images and low signal intensity on T1-weighted images (Figure 4). Longitudinal studies have shown that the presence of bone marrow edema is a key predictor of early erosive joint damage in adult patients with RA. Therefore, bone marrow edema, as well as synovial hypertrophy, are considered to be the most sensitive MRI features for monitoring disease activity in rheumatoid
arthritis (37-40). However, we have no longitudinal studies focused on the prognostic value of bone marrow edema in the development of erosive changes in JIA. The clinical relevance of bone marrow changes in pediatric JIA patients is therefore unclear and might be unrelated to JIA disease activity. Rather, it might be a part of the development of the joint or the patient's biomechanical activity, as expressed by his engagement in sports.

Figure 4. Bone marrow edema. Coronal (a) and sagittal (b) fat saturated T2-weighted images and a sagittal T1-weighted post-contrast MR image (c) obtained in a 15-year old girl without a history of recent trauma show significant bone marrow changes in the trabecular bone of the lateral tibia plateau with ill-defined margins and high signal intensity on T2-weighted fat-saturated images, and low signal intensity on T1-weighted images (arrows).

Cartilage lesions

MRI permits more specific evaluation of articular cartilage as compared to conventional radiography and ultrasonography. MRI allows differentiation between the three histologically distinct types of hyaline cartilage; i.e. epiphyseal, physeal, and articular cartilage. The epiphyseal and physeal types of cartilage are responsible for longitudinal growth, because of enchondral ossification. Articular cartilage protects and nourishes subchondral bone at joint surfaces. It transmits and buffers physiologic and abnormal forces across joints, particularly at weight-bearing sites (41). Articular cartilage, which is a highly organized form of hyaline cartilage, can be seen on T2-weighted images as a thin hyper intense rim surrounding the less well-organized hyaline cartilage of the developing epiphysis (42).

Although rarely seen in very young JIA patients, progressive JIA may lead to the destruction of cartilage. Diffuse cartilage thinning is caused by degeneration of cartilage on the joint surface area through enzymes released from the inflamed synovial membrane or because of subchondral resorption (29). Cartilage lesions may be seen as areas of increased water content, contour abnormalities, defects or thinning. Inflamed immature cartilage in JIA patients may show an
accentuated “spoke wheel” enhancement due to by hyperemia (13). Normal articular cartilage has an intermediate signal on T1- as well as T2-weighted MR images. Cartilage degeneration can be assessed most easily on T2-weighted images in the form of increased signal intensity (Figure 5). The greater thickness of cartilage and its extensive blood supply in growing children suggest a unique self-regeneration potential, which diminishes as the skeleton matures. Dedicated sequences permit accurate assessment of cartilage morphology as well as the detection of subtle surface irregularities and focal cartilage defects. However, in children we need to establish the appearance of normal cartilage with reference to age before using these dedicated sequences (43).

Figure 5. Cartilage lesion. Axial T2-weighted image with fat saturation obtained in a 14-year old boy shows a cartilage lesion retro-patellar with increased signal intensities compared to the adjacent normal cartilage (arrow).

Bone erosions
Erosive disease is associated with poor outcomes in JIA (7). Like cartilage lesions, bone erosions are relatively rare in young patients with JIA, and become more common with age. MRI is the most sensitive imaging modality for the detection of erosive changes in JIA (15, 16). MRI clearly shows the difference between articular cartilage and bone deficiencies. Bone erosion may be seen on T1-weighted images as loss of the normal low signal intensity of cortical bone and loss of the normal high signal intensity of trabecular bone. On T2-weighted images, bone erosions appear as hyper-intense lesions (Figure 6). Erosions have sharp margins. Provided they are localized correctly in the juxta-articular aspect, erosions are marked by a cortical break in at least one plane. However, the high prevalence of bone depressions in healthy children should be kept in mind (44). Findings suggestive of erosive damage should be interpreted with care in children with suspected disease.
General introduction

Secondary findings

In addition to the above mentioned MRI findings, a few other features may be found in children with JIA. These secondary findings, including joint effusions, tendinopathy, internal derangement, popliteal lymph nodes, and heterogeneity of the infrapatellar fat pad, will be reviewed in greater detail below. Although most of these findings can be observed quite often in JIA patients, they are – as discussed in Chapter 3 – of questionable value for the evaluation of disease status.

Joint effusion

As shown in Chapter 3, joint effusions can be frequently found in JIA patients (29). On MRI it has high signal intensity on T2-weighted images and low signal intensity on T1-weighted images. They are predominantly located in the suprapatellar recesses and central recesses (Figure 7). Joint effusions can frequently be seen in both clinically active and clinically inactive JIA patients. Moreover, the presence of joint effusions in healthy children is also reported to be relatively high (44, 45).

Tendinopathy / internal derangement

Synovitis can cause damage and atrophy of tendons, ligaments and menisci (13, 29). The cruciate ligaments can be mildly or severely atrophic and synovial hypertrophy extending over the surface of the menisci can cause degradation (29). These findings occur more often in poorly controlled JIA patients with longstanding disease (17). In Chapter 3 we showed that the presence of tendinopathy or internal derangement in JIA patients with a regular follow-up is rare. Moreover, we found that the assessment of tendinopathy/internal derangement in JIA is difficult and moderately reliable.
Figure 7. Joint effusion. Axial (a) and sagittal (b) fat saturated T2-weighted images obtained in a 16-year old male show a marked joint effusion in the suprapatellar recesses (black arrows). Furthermore, even without Gd synovial hypertrophy can be seen in the suprapatellar recesses, the infrapatellar fat pad and adjacent to the medial posterior condyle of the femur (white arrows).

Popliteal lymph nodes
As described in Chapter 3, popliteal lymph nodes can be seen very often in pediatric JIA patients (Figure 8), and their presence or volume does not correlate with the presence of synovitis (29). Moreover, the presence of popliteal lymph nodes is age-related, with a higher frequency at a young age (46). The presence of popliteal lymph nodes is not associated with inflammatory disease (46), and can therefore not be used as a secondary sign of disease activity in JIA.

Figure 8. Popliteal lymph nodes. Sagittal fat saturated T2-weighted image (a) and a sagittal T1-weighted post-contrast MR image (b) obtained in a 10-year old girl show lymph nodes with high signal intensity on T2-weighted and low signal intensity on T1-weighted MR images (arrows).

Infrapatellar fat pad heterogeneity
Infrapatellar fat pad (Hoffa’s fat pad) heterogeneity correlates with synovial thickness in early JIA (29). Fat pad heterogeneity can be caused by water infiltration or by scar tissue. On MRI, water infiltration of the infrapatellar fat pad is depicted as areas of decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted fat saturated images (Figure 9), whereas infiltration of the infrapatellar fat pad by scar tissue shows decreased signal intensity on both T1-weighted and T2-weighted images (Figure 10) (47). Heterogeneity of the infrapatellar fat
pad is more prevalent in children with clinically inactive disease and correlates well with disease duration. As depicted in Chapter 3, fat pad heterogeneity is not related to infiltration of water as a marker of synovitis, but is directly associated with the presence of scar tissue.

**Figure 9.** Infrapatellar fat pad heterogeneity caused by water infiltration. Sagittal fat saturated T2-weighted image (a) and a sagittal T1-weighted post-contrast MR image (b) obtained in a 9-year old girl with clinically active disease show areas of increased signal intensity on the fat saturated T2-weighted image and decreased signal intensity on the T1-weighted image (arrows).

**Figure 10.** Infrapatellar fat pad heterogeneity caused by scar tissue. Sagittal fat saturated T2-weighted image (a) and a sagittal T1-weighted post-contrast MR image (b) obtained in a 15-year old boy in clinical remission with a history of evident knee arthritis show areas of infrapatellar fat pad heterogeneity caused by scar tissue, depicted by decreased signal intensity on both the T2- and T1-weighted images (arrows).

**Scoring methods**

Since the development of highly effective anti-rheumatic therapies, the main goal of treatment is complete suppression of joint inflammation in order to prevent destructive changes. Therefore, outcome measures in clinical routine and clinical trials must include sensitive and reliable measures of inflammation (28). As shown in Chapter 6, a significant number of JIA patients show synovial hypertrophy on MRI despite of normalized clinical and laboratory parameters. Therefore an accurate evaluation of their disease status is warranted (19, 48, 49). The utility of MRI for the assessment of JIA joint pathologies is limited by the fact that there is no generally accepted and easy-to-use MRI scoring system to evaluate disease status in JIA. Consequently, we need validated
scoring measures to accurately measure joint outcomes, and standardize imaging protocols for data acquisition. In Chapter 4 we assessed the reliability and responsiveness of a new Juvenile Arthritis MRI Scoring (JAMRIS) system for evaluating disease activity of the knee. This method has been tested for inter- and intra-reader reliability, and correlates significantly with dynamic contrast-enhanced-MRI parameters. With the JAMRIS system it is possible to distinguish clinically active and inactive JIA patients as shown in Chapter 6, indicating good discriminative value. Furthermore, the JAMRIS system has the advantage that it provides sensitive means of monitoring disease activity in response to therapy, as shown in Chapter 7.

Advanced MRI techniques in JIA
Several advanced MRI techniques are available for the evaluation of inflammatory and destructive changes in JIA. Three of these techniques will be discussed in detail in the following section: dynamic contrast-enhanced MRI, T2-mapping and diffusion-weighted imaging.

Dynamic contrast-enhanced MRI
Synovial hypertrophy is usually evaluated by comparison of T1-weighted images obtained before and after administration of intravenous gadolinium. Although this technique allows direct visualization and measurement of the size and intensity of enhancement of the inflamed synovial membrane, it does not permits quantification of heterogeneous biological activity. Dynamic contrast-enhanced MRI (DCE-MRI) has been suggested as objective imaging bio-marker in JIA as well as in RA, since descriptive DCE-MRI parameters were found to correlate with clinical parameters of disease activity and the degree of histological synovial inflammation (50-54). DCE-MRI is the time-dependent registration of changes in MRI signal during and after the injection of an intravenous contrast agent, resulting in time-intensity curves (TICs). The TIC shape represents characteristics of the tissue, such as vascularization, tissue perfusion, capillary permeability and interstitial space volume, and can be post-processed either by using semi-quantitative descriptive parameters or pharmacokinetic modeling.

We recently developed an DCE-MRI analysis method based on a three-dimensional pixel-by-pixel classification, which helps to visualize differently shaped TICs within a specific volume of interest (55). Compared to the semi-quantitative descriptive or pharmacokinetic modeling analysis methods, this technique is less computationally demanding and more reliable, because it does not make use of model assumptions or non-linear fitting. This DCE-MRI pixel-by-pixel analysis method proved to be feasible in RA, and valuable in distinguishing RA patients from healthy controls or non-RA patients (56, 57). In Chapter 9 we assessed the discriminative value of this
DCE-MRI pixel-by-pixel analysis method by comparing semi-quantitative descriptive DCE-MRI parameters and the relative number of TIC shapes as derived from DCE-MRI between knees of clinically active and clinically inactive JIA patients.

**T2-mapping**

T2-mapping is a parametric technique that can be easily implemented to assess cartilage morphology, in terms of cartilage hydration or collagen orientation. Cartilage is divided into normal, immature and diseased types (58, 59). There is a general decrease in T2 relaxation from the cartilage surface to the deeper layers, but cartilage degradation which accompanies JIA has been shown to increase on T2 compared to age-matched controls (59, 60). T2-mapping is performed before intravenous injection of gadolinium to prevent the effects of T1- and T2-shortening.

Other techniques that may be used to evaluate cartilage include contrast-free T1-rho or delayed gadolinium-enhanced MRI of cartilage (dGEMRIC). These techniques permit evaluation of the proteoglycan content, which is important in adults with regard to cartilage stiffness, and may be reduced in the presence of disease. However, the significance of proteoglycan abnormalities in children with JIA is unclear.

**Diffusion-weighted imaging**

Diffusion-weighted imaging (DWI) utilizes the random motion of water molecules. The motion of water would be entirely random in a totally unrestricted environment, such as Brownian motion or free diffusion. Water does not move in completely random fashion within tissue, but is hampered by interaction with tissue compartments, cell membranes, and intracellular organelles (61). The extent of tissue cellularity and the presence of intact cell membranes help to determine the impedance of water molecule diffusion. Tissue types reported to be associated with impeded diffusion include tumor, cytotoxic edema, abscess, and fibrosis. Tissues with low cellularity or tissue consisting of cells with disrupted membranes permit greater movement of water molecules (61).

DWI is primarily used in neurologic and oncologic diseases, although it can be used to evaluate musculoskeletal pathology as well (62, 63). In adults DWI performed as well as T1-weighted contrast-enhanced MRI for the evaluation of synovial hypertrophy. Although DWI is considered valuable for the assessment of cartilage, it is limited by the short T2-relaxation time of cartilage (60). The contrast-free approach of DWI is important and desirable, but difficulties concerning its implementation and analysis currently limit the value of this technique in clinical routine and trials.
Pitfalls

MRI offers excellent insight into the dynamic process of maturation and growth of the skeleton. As growing joints change, it may be difficult to establish whether differences in the appearance of the knee joint are pathological or a part of normal development. Some appearances of bone, bone marrow and cartilage may look pathological, but may be merely signs of physiological growth. Some of these pitfalls will be discussed in the following section.

Ossification variants

Differentiating ossification variants from pathological conditions – such as osteochondritis dissecans or defects of cartilage or bone – on MRI is challenging. In the distal femur, ossification usually starts in the center of the cartilaginous epiphysis (64). As the newly formed ossification center contains hematopoietic (red) bone marrow, its signal intensity will be the same as that of red marrow in the adjacent distal femoral metaphyses (33). The ossification center enlarges due to enchondral bone development. Adjacent cartilage cells undergo hypertrophy during the enchondral ossification which results in increased signal intensity on T2-weighted images (42). This area of high signal intensity is most apparent in the posterior part of the distal femoral epiphysis and can be quite discrete (Figure 11) (45).

Figure 11. Enchondral ossification. Sagittal fat saturated T2-weighted image obtained in a 5-year old boy shows an area of high signal intensity in the posterior part of the distal femoral epiphysis (arrows) due to hypertrophy of cartilage cells during enchondral ossification.

There is a high prevalence of ossification variants of the femoral condyle among boys aged 2–12 years and girls aged 2–10 years: this should not be considered abnormal (45). Spiculation or small foci of bone are caused by ossification variants (45, 65, 66). When the variant is located within the ossified part of the epiphysis, a focal defect of subchondral bone can be seen. Ossification variants are categorized as follows: 1. a puzzle piece defect is completely filled by bone, 2. a partial puzzle piece is partially filled by bone, 3. irregular subchondral bone plate is seen in spiculated ossification variants, and 4. extra ossification centers may occur in the non-ossified
physeal cartilage (65, 67). An overview of these ossification variants is depicted in Figure 12. These areas of irregular ossification can be confused with osteochondritis dissecans and cartilage/bone lesions in the scope of JIA, especially along the ossifying margins of the distal femoral condyles (67). The lack of bone marrow edema in the adjacent epiphysis and a more posterior location are signs of normal development (Figure 13) (65, 67). Ossification variants can regress spontaneously and do not evolve into osteochondritis dissecans (67). An example of a case with osteochondritis dissecans is depicted in Figure 19. Notice that bone marrow edema is present adjacent to the lesion (Figure 14). This is in contrast to the patient with an ossification variant with no bone marrow edema (Figure 13).

**Figure 12.** Ossification variants. (a) a puzzle piece defect is completely filled by bone, (b) a partial puzzle piece is partially filled by bone, (c) irregular subchondral bone plate is seen in spiculated ossification variants, and (d) extra ossification centers may occur in the non-ossified physeal cartilage.

**Figure 13.** Ossification variant. Sagittal T1-weighted post-contrast (a, c) and sagittal fat saturated T2-weighted images (b, d) obtained in an 11-year old boy show irregular ossification along the ossifying margins of the distal femoral condyle without any accompanying bone marrow edema (arrows at upper two images). The images of the same boy 1.5 years later show a regression of the ossification variant (arrows at lower two images).
Figure 14. Osteochondritis dissecans. Sagittal T1-weighted post-contrast (a) and sagittal fat saturated T2-weighted images (b) obtained in a 15-year old girl show a lesion in the distal femoral condyle (white arrows), with marked bone marrow edema (black arrows) and signal intensity changes of the adjacent cartilage.

**Cortical desmoid**

A cortical desmoid is frequently observed in older children and adolescents. It is a benign self-limiting fibrous or fibro-osseous lesion usually at a distal posterior location of the medial femoral meta-epiphysis, and should not be confused with an inflammatory or destructive lesion in the scope of JIA. Cortical desmoids are considered to be a result of repetitive traction from the medial head of gastrocnemius or the aponeurosis of the adductor magnus at their attachment site. Usually the asymptomatic lesions are incidentally found on conventional radiographs or MRI’s. On conventional radiographs its incidence is reported to be 11.5% for males and 3.6% for females (68). However, MRI is more sensitive in the detection of these cortical lesions (69). Typically the cortical desmoids are 1 to 3 cm in size and of irregular shape. The lesions are hyper-intense on T2-weighted images and of low signal intensity on T1-weighted images without accompanying bone marrow edema (Figure 11). On conventional radiographs a cortical desmoid will appear as an area of cortical irregularity or roughening at the typical location of the posteromedial cortex of the distal femoral meta-epiphysis (Figure 15) (68).

Figure 15. Cortical desmoid. Sagittal T1-weighted post-contrast (a), sagittal fat saturated T2-weighted images (b) and a conventional radiograph (c) obtained in a 15-year old girl show a cortical desmoid in the distal posterior medial femoral meta-epiphysis with low signal intensity on the T1-weighted image and hyper-intense signal intensity on the T2-weighted image (arrows). There is no accompanying bone marrow edema. On the conventional radiograph, the cortical desmoid appears as an area of cortical irregularity or roughening (arrow).
Bone marrow appearances

The anatomy of joints changes during growth, thus making it difficult to differentiate between knee joint pathologies and normal maturation. One of the difficulties is to differentiate between normal bone marrow and pathological changes in bone marrow. As mentioned previously, the transformation from hematopoietic to fatty bone marrow continues in the diaphysis and proceeds towards the metaphyses (32). Zones of hematopoietic red bone marrow in the distal diaphysis and metaphysis of the femur may be seen as ‘flame-like’ regions with high signal intensity on T2-weighted fat-saturated images and low signal intensity on T1-weighted images (Figure 16). Typically, these marrow ‘flames’ have a base at, or adjacent to, the physis, and straight vertical margins (42). As the last parts to convert are the proximal humeral and femoral metaphyses, these hematopoietic bone marrow ‘flames’ can be seen into early adulthood at these locations (34-36).

Figure 16. Hematopoietic red bone marrow ‘flames’. Coronal fat saturated T2-weighted (a) and coronal T1-weighted post-contrast images (b) obtained in an 8-year old girl show ‘flame like’ regions of hematopoietic red bone marrow with high signal intensity on the T2-weighted image and low signal intensity on the T1-weighted image. The marrow ‘flames’ have a base at the physis and are characterized by straight vertical margins.

Speckled bone marrow is another normal variant that may be mistaken for pathology. Changes in the form of speckled bone marrow include small spots of high signal intensity on T2-weighted fat-saturated images and low signal intensity on T1-weighted images, predominantly located in the feet and ankle of children younger than 15 years of age (70), although it may also be seen in the tibial plateau and the distal epiphysis of the femur as well (Figure 17). The speckled appearance may be caused by focal regions of residual hematopoietic bone marrow or physiological stress, possibly related to weight-bearing or altered biomechanics during normal growth (70).
Figure 17. Speckled marrow appearance. Coronal and sagittal T2-weighted fat saturated MR images obtained in a 10-year old boy show spots of high signal intensity on the T2-weighted images in both the tibia plateau and the epiphysis of the femur (arrows).
References

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