Innovating imaging in juvenile idiopathic arthritis: an ongoing quest

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Citation for published version (APA):
Chapter 1

General introduction and outline of the thesis

This chapter is adapted from:
1 – GENERAL INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common cause of joint inflammation in childhood. It comprises all forms of childhood arthritis that start before the age of 16 years, persist for more than 6 weeks and are of unknown etiology. The prevalence in the Western population is estimated to be 1 in 1000 children [1]. JIA is characterized by inflammation of the synovium, which can eventually lead to damage of the osteochondral structures such as joint cartilage and bone.

Classification

JIA is classified into seven categories according to the ‘International League of Associations for Rheumatology’ (ILAR) criteria, aiming to create homogeneous subgroups: systemic JIA (sJIA), oligoarticular JIA, rheumatoid factor (RF) negative polyarticular JIA, RF-positive polyarticular JIA, enthesitis related arthritis (ERA), psoriatic arthritis and undifferentiated JIA (Table 1) [2].

The classification based on the ILAR criteria was expected to enable adequate prediction of the disease course and appropriate therapy decisions. However, up until today, the classification has not proved its added value for prognosis or treatment decisions yet. This is caused by several factors. First of all, there is a considerable amount of overlap between the categories, which hampers the classification into unique stand-alone categories. Some of the categories are very much alike, for example the oligoarticular and polyarticular JIA, which are differentiated only based on a cut-off value for the number of clinically affected joints [3]. Secondly, the criteria on which the classification is made, are under debate. The presence of antinuclear autoantibodies is completely left out of the ILAR classification, despite strong evidence that this marker is associated with a specific disease course and risk for complications [4]. Another issue is the sJIA category, which turned out to have a completely different pathogenesis and clinical presentation than the other JIA categories. Therefore sJIA is often considered to be a completely unique and separate entity in the current JIA classification [5].

Pathogenesis

The pathogenesis of JIA is not entirely known, but recent studies have provided a lot of new insights. Besides the genetic factors, environmental factors, such as infections, are involved with the development of JIA, although unambiguous prove is still lacking [1].

The role of genetics is illustrated by twin studies with a concordance of 25-40% [6]. Furthermore, the association between HLA-genes and different JIA categories has been established, such as the association of HLA-B27 and ERA [1]. Also, several non-HLA-genes,
for example PTPN22, IL2RA, IL2-IL21, STAT4, CD247 and the TRAF1/C5-gene region, appear to be associated with JIA. These genes encode for proteins which are involved in different immunological processes [7-9]. International collaborations currently lead to the evaluation of large populations of JIA patients in ‘genome wide association studies’, eventually leading to identification of other involved genes [7]. Currently, it is estimated that 20-25% of the risk to develop JIA is attributable to the known HLA-regions and non-HLA loci [9].

Table 1 | The different categories of juvenile idiopathic arthritis based on the ILAR-criteria [2]

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
<th>Part of JIA; Start age; years</th>
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<tbody>
<tr>
<td>systemic JIA</td>
<td>arthritis and fever &gt; 2 weeks with rash, generalized lymphadenopathy, hepatomegaly, splenomegaly or serositis</td>
<td>4-17 through childhood</td>
</tr>
<tr>
<td>oligoarticular JIA</td>
<td>arthritis in 1-4 large joints during first 6 months of the disease; 60-80% of these patients is ANA-positive</td>
<td>27-60 early childhood, peak 2-4</td>
</tr>
<tr>
<td>persistent</td>
<td>arthritis in ≤ 4 joints during the disease course after first 6 months</td>
<td>40</td>
</tr>
<tr>
<td>extended</td>
<td>arthritis in &gt; 4 joints during the disease course after first 6 months</td>
<td>20</td>
</tr>
<tr>
<td>RF-negative RA</td>
<td>arthritis in ≥ 5 joints, symmetric presentation; RF serology tests are negative</td>
<td>11-30 early peak 2-4; late peak 6-12</td>
</tr>
<tr>
<td>RF-positive RA</td>
<td>arthritis in ≥ 5 joints, ≥ 2 positive tests for RF with at least 3 months interval; symmetrical involvement of small and large joints; frequently accompanied with bone erosions</td>
<td>2-7</td>
</tr>
<tr>
<td>psoriatic arthritis</td>
<td>arthritis and psoriasis, or arthritis with ≥ 2 of the following: dactylitis, nail pitting/onycholysis or psoriasis in first degree relative</td>
<td>2-11 early peak 2-4; late peak 9-11</td>
</tr>
<tr>
<td>enthesitis-related arthritis (ERA)</td>
<td>arthritis and enthesitis, or arthritis or enthesitis alone with ≥ 2 of the following: SI-joint tenderness, inflammatory lumbosacral pain, HLA-B27 genotype, onset in boys ≥ 6 year, acute anterior uveitis, or HLA-B27-associated diseases associated* in first degree relatives</td>
<td>1-11 late childhood or adolescence</td>
</tr>
<tr>
<td>undifferentiated arthritis</td>
<td>arthritis that does not meet the criteria of any of the above category or more than one category</td>
<td>11-21</td>
</tr>
</tbody>
</table>

JIA = juvenile idiopathic arthritis; ILAR = International League of Associations for Rheumatology; ANA = antinuclear autoantibody; RF = rheumatoid factor; SI = sacroiliac.

* For example ankylosing spondylitis (Bechterew’s disease), sacroiliitis or arthritis in inflammatory bowel disease (IBD), Reiter’s syndrome, and acute anterior uveitis (AAU).
The underlying immunological mechanisms differ per JIA category. In sJIA the innate immunesystem of macrophages is activated. This leads to increased cytokine levels of interleukin(IL)-18, IL-1 and IL-6 [1]. The impaired function of the natural killer cells appears to be specific for sJIA and possibly plays a role in the development of the macrophage activation syndrome [10]. The underlying mechanisms in the other JIA categories, like oligo- and polyarticular JIA, seem to be based on an impairment in the adapted immune system, resulting in activated, autoreactive T-cells [1]. Genetic research has also underlined the importance of the regulation of T-cell growth factor IL-2, which determines the balance between T-cell activation and immune tolerance [9].

The findings on molecular level go hand in hand with the developments on new treatment strategies, as explained further in the ‘Treatment’ part of the introduction. Recent evidence showed that increased levels of biomarkers S100A12 and MRP8/14 caused by activated granulocytes and macrophages clearly indicates their direct involvement in the inflammation in JIA. These biomarkers are thought to be more sensitive for disease activity than erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels [11].

Diagnostics

The first presentation of JIA is very heterogeneous, which is also illustrated by the different above-mentioned JIA categories based on the ILAR criteria.

In general, JIA is a ‘diagnosis-per-exclusionem’, which is made based on clinical characteristics after the exclusion of other causes (Table 2). There is no gold standard for JIA. The patient’s history and the clinical findings of the physical examination are the primary parameters for diagnosis; important clues for the diagnosis are described in Table 3.

JIA and rheumatoid arthritis (RA) in adults are different diseases. The most important difference is the age of onset. In contrast to the involvement of the small joints of the hand and foot in RA in adults, the target joints in JIA consist most frequently of the knee, ankle and wrist [12]. Whereas in the blood of RA patients both autoantibodies against cyclic citrullinated peptide (CCP) or RF are found in 70-80% of the patients, antinuclear antibody (ANA) is the more common autoantibody in JIA (present in approximately 75%) [4,13]. The presence of autoantibodies is not specific for RA or JIA.

Through the years, several outcome measures have been developed to quantify the disease activity in JIA patients. These outcome measures are increasingly used in research settings and in daily practice [14]. A promising clinical JIA outcome measure is the ‘Juvenile Arthritis Disease Activity Score’ (JADAS), which consists of the following 4 variables:
global assessment of disease activity of the physician on a visual analogue scale (VAS); global assessment of well-being of the patient on a VAS, number of active joints, and the normalized ESR ([ESR (mm/h) 20]/10) [14].

Table 2 | Differential diagnosis for arthritis in children

<table>
<thead>
<tr>
<th>Category*</th>
<th>Examples of diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>infectious arthritis, osteomyelitis</td>
<td>Lyme's disease, mycobacterial infections</td>
</tr>
<tr>
<td>para- or postinfectious arthritis</td>
<td>streptococcal infection, viral infections</td>
</tr>
<tr>
<td>orthopedic disorders</td>
<td></td>
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<tr>
<td>juvenile idiopathic arthritis</td>
<td></td>
</tr>
<tr>
<td>arthritis in other autoimmune diseases</td>
<td>SLE, psoriasis</td>
</tr>
<tr>
<td>arthritis in other autoinflammatory diseases</td>
<td>inflammatory bowel disease</td>
</tr>
<tr>
<td>hematological causes</td>
<td>intraarticular hemorrhage in hemophilia, sickle cell disease</td>
</tr>
<tr>
<td>malignancies in the joints</td>
<td>leukemia, lymphoma, solid tumors</td>
</tr>
<tr>
<td>metabolic disorders</td>
<td>mucopolysaccharidosis</td>
</tr>
<tr>
<td>other causes</td>
<td>sarcoidosis, immune deficiencies, juvenile hemochromatosis</td>
</tr>
</tbody>
</table>

SLE = systemic lupus erythematosus  
* The diagnoses are in order of likelihood

Table 3 | Important aspects of patient history and physical examination in JIA

<table>
<thead>
<tr>
<th>Category</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>patient history</td>
<td></td>
</tr>
<tr>
<td>complaints</td>
<td>joint pain, -swelling and -stiffness, morning stiffness</td>
</tr>
<tr>
<td>daily activities</td>
<td>impairment of movement, dependent on help</td>
</tr>
<tr>
<td>family</td>
<td>autoimmune diseases and inflammatory diseases such as RA, IBD, SpA, psoriasis, uveitis and thyroid diseases</td>
</tr>
<tr>
<td>physical examination</td>
<td></td>
</tr>
<tr>
<td>general inspection of the musculoskeletal system</td>
<td>pain during examination, limitation of movement, decreased strength, muscle atrophy, bone deformities, dactylitis, nail abnormalities and enthesitis</td>
</tr>
<tr>
<td>joints</td>
<td>warmth, pain or swelling of joints, number of inflamed joints</td>
</tr>
<tr>
<td>systemic characteristics</td>
<td>fever, lymphadenopathy, hepatosplenomegaly, rash</td>
</tr>
<tr>
<td>growth parameters</td>
<td>length, weight, growth curve</td>
</tr>
<tr>
<td>other observations</td>
<td>gait and leg length discrepancy</td>
</tr>
</tbody>
</table>

JIA = juvenile idiopathic arthritis; RA = rheumatoid arthritis; IBD = inflammatory bowel disease; SpA = spondyloarthropathy
These variables for disease activity will change in the future. As mentioned before, new biomarkers such as MRP8/14 and S100A12 are more sensitive than ESR or CRP [11]. Additionally, expect an important role for imaging in the assessment of disease activity in patients with JIA.

**Imaging**
Subtle arthritis can be difficult to detect with physical examination. Furthermore, changes over time in disease activity in certain joints can be very hard to monitor clinically. Therefore, imaging plays an increasingly important role in the diagnosis, monitoring of disease activity and response to therapy in patients with JIA.

Nowadays, conventional radiography has limited added value in JIA: adequate evaluation of soft tissue is difficult and structural osteochondral damage is only visible in a late stage. Advantages of conventional radiography include the widespread availability, low costs and validated scoring systems for the evaluation of damage and growth (e.g. the ‘Dijkstra score’) [15]. Currently, the main strength and use of conventional radiography in the management of JIA patients is the monitoring of skeletal development by means of an hand radiograph.

Both ultrasound and magnetic resonance imaging (MRI) are able to depict the primary target of the disease, the synovial membrane. Ultrasound is superior to physical examination in the non-invasive detection of synovitis. Additionally, ultrasound can be helpful for the guidance of intra-articular injections.

MRI has a high sensitivity for the detection of arthritis in all target joints, even for (subclinical) arthritis in the temporomandibular joint of JIA patients [16]. MRI with intravenous contrast administration enables adequate depiction of inflammation of the synovium and tendons, but also of bone marrow edema, bone erosions and cartilage lesions (Figure 1). Objective, radiation-free and multiplanar imaging of all involved structures in JIA is only able with MRI [15].

Recent studies within the field of MRI in JIA showed that the use of MRI in children is feasible, particularly when scanning only the most affected joint (and not bilaterally). Unilateral scanning is sufficient in JIA patients, provided that an intravenous contrast agent is used [17]. Besides good feasibility, the standardization of the MRI evaluation by means of the Juvenile Arthritis MRI Scoring (JAMRIS) system, have further improved the usefulness of MRI in daily practice. The JAMRIS system proved to be reliable and responsive to change [18].
Figure 1 | (a) Midsagittal T1-weighted MR image of the knee of a JIA patient before intravenous contrast administration. (b) Corresponding schematic representation to (a) with the following anatomical structures: 1=patellar tendon, 2= patella, 3=femur, 4=growth plate, 5=tibia. (c) Superior and posterior to the patella and centrally in the knee several hyperintense areas are visible on sagittal T1-weighted MR image of the knee after the administration of intravenous contrast, representing enhancement of the thickened synovium. (d) Corresponding schematic representation with the green areas highlighting the areas that enhance after intravenous contrast administration.
Complications
The most common complications of chronic arthritis in JIA are growth disturbances of the joints, varying from local accelerated bone maturation to overall growth retardation. Micrognathia or leg-length discrepancies may be consequences of early closing of the epiphyses caused by local inflammation in the joint.

Anterior uveitis is another commonly diagnosed complication in JIA (and not in RA), which is predominantly present in the ANA-positive patients. In extreme cases, this uveitis can lead to blindness. Therefore, JIA patients should be regularly screened (at least once per year) by the ophthalmologist according to a standardized protocol [19].

An acute and potentially life-threatening complication of sJIA is the macrophage activation syndrome. This syndrome is characterized by hemophagocytosis and can result in pancytopenia, hemorrhages based on disseminated intravascular coagulation and (multiple) organ failure [5].

Treatment
During the past decennia the treatment of JIA has significantly improved. The major goal of treatment is achieving and maintaining clinical remission. The Wallace criteria (Table 4) are used to determine whether a patient is in clinical remission [20]. Besides medication, occupational therapy, and psychosocial support are important pillars in the management of JIA [1]. In current practice, non-steroidal anti-inflammatory drugs (NSAIDs) are very commonly used [1,21]. Intra-articular glucocorticoid injections are considered effective in case of monoarthritis or persistent oligoarthritis [1].

When the disease activity persists, disease modifying antirheumatic drugs (DMARDs) will be initiated. The most commonly chosen DMARD is methotrexate (MTX), followed by sulphasalazine and leflunomide [21]. MTX is administered orally or subcutaneously once per week and the supplementation of folic acid is advised to prevent liver enzyme abnormalities and bone marrow depression [1].

The working mechanism of biologicals is based on the inhibiting of cytokines which play a key role in the pathogenesis of JIA. A biological is started when MTX insufficiently reduces the disease activity or in case of medication intolerance [22]. Most of the biologicals (etanercept, adalimumab and infliximab) target the inhibition of tumor necrosis factor alfa (TNF-α). In the treatment of sJIA, the inhibition of IL-1 (by anakinra and canakinumab), IL-6 (by tocilizumab) and activated T-cells (by abatacept, in persisting polyarthritis) has proven to be effective. These new treatment regimens will reduce the use of systemic glucocorticoids [21,23,24].
Table 4 | ACR-criteria for inactive disease and the Wallace-criteria for clinical remission in patients with JIA [20,28]

<table>
<thead>
<tr>
<th>ACR-criteria for inactive disease in JIA</th>
<th>Wallace-criteria for remission in JIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No joints with active arthritis^</td>
<td>Clinical remission on medication</td>
</tr>
<tr>
<td>No fever, rash, serositis, splenomegaly or generalized lymphadenopathy caused by JIA</td>
<td>If the ACR-criteria are fulfilled for 6 continuous months while the patient uses medication</td>
</tr>
<tr>
<td>No active uveitis following the definition of the SUN Working Group^</td>
<td>Clinical remission off medication</td>
</tr>
<tr>
<td>If the ACR-criteria are fulfilled for at least 12 continuous months while the patient uses no medication for arthritis or uveitis</td>
<td></td>
</tr>
<tr>
<td>ESR and CRP are not elevated by JIA</td>
<td></td>
</tr>
</tbody>
</table>

Global disease activity by physician is minimal

Morning stiffness 15 minutes or less

ACR = American Congress of Rheumatology; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; JIA = juvenile idiopathic arthritis.

^ Following the definition, active arthritis is present when a joint is swollen, which is not caused by a mass, or if a joint without swelling has limitation of movement or pain.

^ The Standardization of Uveitis Nomenclature (SUN) Working Group defines inactive uveitis anterior as < 1 cell in field sizes of 1mm by a 1-mm slit beam.

The medication treatment regimens are schematically visualized in Figure 2; specific patient characteristics, disease activity and presence of risk factors are taken into account [22]. Currently, the timing of starting consecutive drugs in JIA is a point of debate. Early and aggressive intervention with DMARDs and biologicals are more and more preferred, in order to prevent damage and growth abnormalities of the joints [21]. Also, the development of clear ‘stop-strategies’ are considered a priority in research. It has already been shown that longer treatment with DMARDs after achieving clinical remission does not reduce the chance of flaring [25]. In the future, the decision to stop or decrease the use of medication in JIA patients, is most likely to be based on new biomarkers, such as imaging, molecular testing and serum proteins.

Prognosis

The course of JIA varies strongly between the different categories and individual patients. About 30% of the patients with oligoarticular JIA will be in permanent remission after treatment, just like a part of the patients with sJIA. Half of the patients that do not achieve permanent remission are expected to suffer from JIA during the rest of their lifetime, though often with long periods of inactive disease.

Nowadays, the time to stop treatment after achieving remission is a point of debate in JIA clinical practice. Overall, inactive disease is reached in 40-60% of the patients and the medication is often stopped after 6-12 months of inactive disease [1]. One year
after stopping treatment, approximately half of the patients flares, whereas 75% has flared within 2 years after stopping treatment [25-27]. Biomarkers such as MRP8/14 and subclinical synovitis on MRI can be helpful in the prediction of relapse and thereby in treatment decisions. This possibly leads to a significant reduction in the percentage of patients who will flare after stopping their medication.

Figure 2 | Simplified visualization of the treatment of patients with JIA, based on a previously published flowchart [21]. The number of involved joints determines the category of the patient. The category extended oligoarthritis is classified under polyarticular disease in this flowchart.

In the current daily practice, severe functional disabilities are seen in less than 10% of the JIA patients [26]. Predictors for long-term severe disease course and outcome are polyarthritis in sJIA patients, symmetrical joint involvement, early wrist- or hip involvement, RF- or CCP-positive serology and early abnormalities on conventional radiographs of the joint [27].
2 – OUTLINE OF THE THESIS

In this thesis we aim to elucidate the ongoing quest of imaging in JIA, in order to increase the added value of imaging techniques in the management of patients with JIA. The thesis is divided into three parts: the first part covers topics that simultaneously apply for the knee and wrist, the second part focuses on the knee and the third part on the wrist.

PART I – Knee and wrist
Chapter 2 describes the progress of validating standardized scoring systems for MRI in JIA within the international collaborative initiative between the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) MRI in JIA Working Group and the Health-e-Child Radiology group.

In Chapter 3 we assess the incidence and distribution pattern of the imaging features on MRI of the knee and wrist, thereby providing the daily practice radiologist with a useful tool for the evaluation of MRI in JIA.

PART II – Knee
In Chapter 4 we compared the enhancing synovium on MRI of the knee of children unaffected with clinical arthritis with MRI of the knee of clinically active JIA patients. This comparison increased our knowledge with respect to the normal appearance of the synovium on MRI after intravenous contrast administration and the differences with JIA.

The predictive value of an advanced MRI technique called dynamic contrast-enhanced MRI of the knee is assessed in Chapter 5. We focused on the ability to predict flare in clinically inactive JIA during a 2-year follow-up based on the characteristics of the dynamic contrast-enhanced MRI.

PART III – Wrist
In Chapter 6 we elaborated on the use of the same technique (dynamic contrast-enhanced MRI) in JIA patients with wrist involvement. Both the feasibility and differences as detected by this technique between clinically active and inactive patients were assessed.

Besides the role of MRI in the management of JIA, we also evaluated a new tool which was based on conventional hand radiographs. This automated method called BoneXpert determines bone age based on the size of the carpal and phalangeal bones in the hand and bone health based on cortical thickness of the three midmetacarpals of the hand.
In **Chapter 7** we assessed the feasibility, reproducibility and described bone age and bone health in a cohort of JIA patients using biologicals.

In **Chapter 8** a comparison was made between dual x-ray energy absorptiometry, as the most used technique to determine bone health, and BoneXpert, as a novel automated method.

In **Chapter 9** our ongoing international collaboration initiative summarized several requisites and recommendations for a standardized MRI protocol for the wrist of JIA patients.
REFERENCES

3. Martini A. Are the number of joints involved or the presence of psoriasis still useful tools to identify homogeneous disease entities in juvenile idiopathic arthritis? J Rheumatol 2003;30(9):1900-3.


