ADVANCES IN ULTRASOUND APPLICATION IN JUVENILE IDIOPATHIC ARTHRITIS

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Juvenile idiopathic arthritis (JIA) is a potentially debilitating disease of early childhood. To diagnose JIA pediatric rheumatologists rely on physical examination but there is an increased interest of using the ultrasound (US) because of its advantages over other imaging techniques used in pediatric, which include non-invasiveness, rapidity of performance, ease of repeatability, high patient acceptability and lack of exposure to ionizing radiation. Omeract Ultrasound Task Force has done a great deal of effort and activity to standardize and validate the US image acquisition, define synovitis features and scoring of US abnormalities in children. Current evidences about application of ultrasound in JIA can improve definition of remission necessary to optimize treatment strategies. Ultrasound showed to be reliable while the next step should be to test sensitivity to change in order to possibly be used as an outcome tool in JIA. Due to peculiarities of US examination and image acquisition in children additional educational efforts among pediatric rheumatologists are required for expanding this imaging modality in daily practice.

Descriptors: JUVENILE IDIOPATHIC ARTHRITIS, ULTRASOUND, CHILD

Background

Juvenile idiopathic arthritis (JIA) is the most common chronic arthritis in childhood with potentially significant physical and psychological disability (1). At this time, pediatric rheumatologists rely on physical examination to diagnose JIA. Ultrasound (US) is more sensitive than physical examination while there is an increased interest of using the ultrasound in JIA evaluation since it may detect early disease (2-4). Early detection and treatment of JIA may prevent and/or delay adverse outcomes such as joint damage and disability.

Until now, researches were forced to use the Outcome Measures in Rheumatology (OMERACT) definitions for synovial components and quantification of severity and extent of synovitis developed for adults with rheumatoid arthritis (5). However, these definitions may not be necessarily applicable to pediatric patients, owing to the unique features of the growing skeleton and the changes in joint morphology during development. To overcome the gap...
of standardization and scientific knowl-
dge between adult and pediatric rheuma-
tology, a pediatric US subgroup within the
Omeract Ultrasound Task Force has been
recently founded (6). In addition, the Eu-
ropean League Against Rheumatism (EUL-
AR) involved pediatric rheumatologists
in a project to develop recommendations
for the use of different imaging modalities
in JIA clinical practice (7). EULAR-PReS
encourages considering of using imaging
in the diagnosis and management of juve-
nile idiopathic arthritis in clinical practice
are presented in Table 1.

Why ultrasound in JIA

US has several advantages over
other imaging techniques for use in pedi-
atic subjects, which include non-invasive-
nes, rapidity of performance, ease of re-
peatability, high patient acceptability and
lack of exposure to ionizing radiation (8).
In addition, it does not require sedation for
scanning in younger children. US allows
precise and thorough visualization of in-
flammatory and destructive joint abnor-
malities, including synovial hyperplasia, joint
effusion, cartilage damage, bone erosion,
tenosynovitis and enthesopathy (9).

The classification, treatment stra-
tegy and prognosis of some forms of JIA are
based on the number of joints involved. In
this context US can play a vital role with its
ability to detect subclinical inflammatory
changes in the joints (10). In one study of
early arthritis JIA patients, originally clas-
sified as oligoarticular subtype, US detec-
ted subclinical synovitis in two thirds of the
patients while one third of the patient had
to be reclassified as polyarticular JIA (11).

Table 1
EULAR-PReS points to consider for the use of imaging in the diagnosis and management of juvenile
idiopathic arthritis in clinical practice (7)

<table>
<thead>
<tr>
<th>Point to Consider</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td><strong>US and MRI</strong></td>
<td>are superior to clinical examination in the evaluation of joint inflammation; these techniques should be considered for more accurate detection of inflammation, in diagnosis and assessing extent of joint involvement.</td>
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<tr>
<td>When there is clinical diagnostic doubt, CR, US or MRI can be used to improve the certainty of a diagnosis of JIA above clinical features alone.</td>
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<tr>
<td>If detection of structural abnormalities or damage is required, CR can be used. However MRI or US may be used to detect damage at an earlier time point than CR.</td>
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<tr>
<td>In JIA imaging may be of particular benefit over routine clinical evaluation when assessing certain joints, particularly the use of MRI in detecting inflammation of the TMJ and axial involvement.</td>
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<tr>
<td>Imaging in JIA may be considered for use as a prognostic indicator. Damage on CR can be used for the prediction of further joint damage. Persistent inflammation on US or MRI may be predictive of subsequent joint damage.</td>
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<tr>
<td>In JIA, US and MRI can be useful in monitoring disease activity given their sensitivity over clinical examination and good responsiveness. MRI should be considered for monitoring axial disease and TMJ.</td>
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<tr>
<td>The periodic evaluation of joint damage should be considered. The imaging modality used may be joint dependent.</td>
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<tr>
<td>US can be used for accurate placement of intra-articular injections.</td>
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<tr>
<td>US and MRI can detect inflammation when clinically inactive disease is present; this may have implications for monitoring.</td>
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</table>

CR, conventional radiography; JIA, juvenile idiopathic arthritis; TMJ, temporomandibular joint; US, ultrasound; MRI, magnetic resonance imaging
In adult patients with RA, there is evidence that synovitis detected by imaging may be frequent in patients who meet clinically-defined remission criteria, and is associated with adverse clinical, functional, and structural outcomes (12). This observation has raised a plea with aim to remission defined by imaging. Recent studies in children with JIA have also shown that remission defined by clinical criteria does not always equate to the complete absence of inflammation as measured by new sensitive imaging techniques, such as ultrasound (13, 14). A high prevalence of ultrasound-detected subclinical synovitis was found in joints that were considered normal on clinical examination. However, the clinical significance and prognostic value of these findings is unclear, as the presence of abnormalities on ultrasound, including power Doppler signal, did not predict subsequent synovitis flare.

Nowadays it is widely agreed that the primary target for the treatment of JIA should be a state of clinical remission. Clearly, when remission is interpreted as the complete absence of any measurable sign of disease activity, the definition of inactive disease is most stringent (15). However, achievement (and maintenance) of true inactive disease is still problematic in routine clinical practice in many children with JIA, particularly among those with the most severe forms of disease.

The absence of guidelines or recommendations for US scanning procedure and interpretation of findings in paediatric rheumatology represents a drawback to establish its validity. Lack of standardized precise definitions of grey scale (GS) and Power Doppler (PD) US findings in different age groups was the biggest limitation for its use. Additional difficulty is age dependent variability of normal sonoanatomy, due to maturation and ossification in children (16). That is why acquisition, interpretation and comparison of US images are completely different than in adults and had to be addressed specifically (17). All this may affect the validity of the technique, and without defined standardized examination technique, US can be a challenge in the childhood population. On the other hand, US as an imaging technique is considered to be examiner and equipment dependent. Studies resulting in good intra and inter-reader reliability and validity, based on specific definitions, are essential for its application as a diagnostic tool (18).

**Developments in ultrasound application in JIA**

The Omeract Ultrasound (US) Task Force is an international collaborative group of experts with the aim to investigate applicability of US in pediatric rheumatology and to develop its metric properties. In order to test validity and improve the applicability of US in JIA, the pediatric subgroup in 2012 investigated the usage of the US among pediatric rheumatologists and performed a systematic literature review (SLR). SLR found that although at present US is not widely used by pediatric rheumatologists, there is considerable interest in this imaging technology among pediatric rheumatologists (19).

According to the Omeract applied methodology, definitions of the joint components visualized by ultrasound, as well as their validation, are developed in a multi-step consensus process (20). In the case of pediatric subtask group a panel of international experts in children US were involved. In the 1st step a group of experts are invited to join a web based consensus process in order to develop definitions for the various components of the pediatric joint. All of these experts have extensive experience (2 to 15 years) in MSUS including in children, with the majority being pediatric rheumatologists. All of them have been part of the scientific validation of MSUS previously including participa-
tion in the work of Omeract. In order to agree on a definition ≥80% of participants would need to score the respective definition/component as either 4 or 5 on the Likert scale defined as: 1 strongly disagree, 2 disagree, 3 neutral, 4 agree, 5 strongly agree. In the 2nd step, in face to face meeting, a subgroup of these experts revise the definitions, developed in step 1, covering the specific structures of interest in healthy children or children with juvenile idiopathic arthritis (JIA). In the 3rd step the applicability of the revised definitions is then tested in a live exercise, involving JIA patients or healthy children, organized with aim to test intra and inter-reader reliability. Following standardized image acquisition and machine setting protocol four joints (wrist, 2nd MCP, knee and ankle) are examined in 4 different age groups (toddler and preschool ages 2-4 years, young children ages 5-8 years, preadolescent ages 9-12 years, and teenager ages 13-16 years) of JIA patients or healthy children (21). Percentage agreement is used for analysis of Delphi round results. Kappa values are calculated for all inter- and intra-observer reliability analyses. Kappa coefficients are interpreted according to Landis and Koch (0.81-1 almost perfect, 0.6-0.8 good, 0.41-0.6 moderate, 0.21-0.4 fair, 0.1-0.2 slight, and <0.1 no agreement) (22).

Following described methodology Omeract US pediatric subtask force recently finalized several important studies. In 2014 subgroup first published definitions of the 5 anatomical components of the joints in healthy children (23). There were two main limitation of this first pioneer work: a) assessment of the joint components on B-mode (or gray scale, GS) without using Doppler technique (why the normal vascularisation of healthy joints was not detailed) and b) some anatomical structures, specifically present during childhood were not defined (such as fat pad and cartilaginous structures present in physis and epiphysis). That is why in a subsequent Delphi survey Omeract group provided amendment of the definitions for the US features of the joints in healthy children covering fat pad, vascularization, ossification and physis (manuscript in press). Additionally, the subgroup worked on standardization of the image acquisition for different joints and published recommendations for the four most frequently affected joints in JIA (knee, wrist, ankle and metacarlo-phalangial joint) (21).

The study showed good comparability of images obtained by all examiners despite usage of different US machines, additionally; standard scanning image acquisition was reproducible regardless of child age. Due to the age-related differences in normal US findings in healthy children, the group focused on the presence of physiological vascularization and ossification. Multi-observer reliability exercise study in children with different age groups found out that according to specific joint and age up to 3 solitary PD signals can be detected within the joint due to the physiological vascularization in different age groups localized predominantly in the specific anatomic positions (fat pad, the epiphysis, the physis and the short bone cartilage). Additionally, same study resulted in ossification grade definitions in children (manuscript in press).

In parallel, using Delphi consensus methodology and still image exercise group developed preliminary definitions for synovitis, illustrated in Figure 1 (24). A subsequent JIA patient based exercise with intra and inter-observer reliability study, held in March 2016, resulted in a development of a scoring system for B-mode and Power Doppler grading of synovitis components to be used as a measure of synovitis activity (manuscript in preparation). Reliability exercise proposed 0-3 semi-quantitative B-mode and color power/Doppler US definitions for synovial components and grading. The proposed synovitis grading for children showed to be
Ultrasound has numerous advantages when used to examine joints in children compared to other imaging modalities. In JIA ultrasound is considered particularly useful for its ability to detect subclinical synovitis and improve classification of JIA patients into the subtypes. Current evidences about application of ultrasound in JIA can improve definition of remission necessary to optimize treatment strategies. Ultrasound showed to be reliable while the next step should be testing sensitivity to change in order to be used as an outcome tool in JIA. Due to peculiarities of US examination and image acquisition in children additional educational efforts among pediatric rheumatologists are required for expanding this imaging modality in daily practice.

**Abbreviations:**
JIA - Juvenile idiopathic arthritis
US - ultrasound
OMERACT - Outcome Measures in Rheumatology

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All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

LITERATURE


NAPREDAK U PRIMJENI ULTRAZVUKA U JUVENILNOM IDIOPATSKOM ARTRITISU

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Juvenilni idiopatski artritis (JIA) je bolest koja se javlja u ranom djetinjstvu i može biti uzrok trajnih tjelesnih oštećenja. Prilikom postavljanja dijagnoze JIA pedijatrijski reumatolozi se oslanjaju na fizikalni pregled, ali postoji i sve veći interes za upotrebu ultrazvuka (UZ) kod pedijatrijskih bolesnika radi prednosti koje nudi pred drugim slikovnim pretragama, uključujući neinvazivnost, brzinu pregleda, lakoću ponavljanja pretrage, prihvatljivost pregleda za pacijente, kao i izbjegavanje ionizirajućeg zračenja. Omeract Ultrasound Task Force skupina je uložila veliki napor u standardizaciji i vrednovanju načina obavljanja UZ pretrage, definiranju značajki sinovitisa i ocjenjivanju UZ abnominalnosti kod djece. Postojeći dokazi vezani uz primjenu ultrazvuka u JIA mogu pomoći u unaprjeđenju definicije remisije bolesti nužne za izbor najbolje strategije liječenja. Ultrazvuk se pokazao pouzdanom pretragom i stoga bi sljedeći korak trebao biti ispitivanje osjetljivosti na promjene aktivnosti bolesti, kako bi se mogao koristiti kao alat u procjeni mogućeg ishoda JIA. Zbog specifičnosti UZ pregleda kod djece, trebalo bi uložiti dodatni napor u edukaciju pedijatrijskih reumatologa, kako bi se proširila upotreba ove dijagnostičke pretrage u svakodnevnoj praksi.

Deskriptori: JUVENILNI IDIOPATSKI ARTRITIS, ULTRAZVUK, DIJETE