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IMAGING (D MINTZ, SECTION EDITOR)

Emergence of Musculoskeletal Ultrasound Use in Pediatric Rheumatology

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Abstract

Purpose of Review To summarize recent international efforts on standardization and validation of pediatric musculoskeletal ultrasound and determine its role in diagnosis and monitoring of disease in pediatric rheumatology.

Recent Findings Over the past decade, significant progress has been made on building the evidence base for musculoskeletal ultrasound in pediatric rheumatology. This includes the clear definition of the sonographic appearance of the normal pediatric joint and enthesis on ultrasonography, definitions for pathology, and the establishment of a specific scoring system for the pediatric knee. Ultrasonography has been shown to have an important role in the detection of subclinical synovitis and can predict flares in children considered to be in remission clinically.

Summary Musculoskeletal ultrasound is likely going to play an important role in complementing the clinical exam especially in juvenile idiopathic arthritis. Given the powerful therapeutic tools available, it will support early diagnosis and precisely determine remission status. In a treat to target approach, it will greatly help to define the targets that need to be reached.

Keywords Musculoskeletal ultrasound · Pediatric rheumatology · Semiquantitative scoring · Subclinical synovitis · Enthesitis

Introduction

Musculoskeletal Ultrasound and Pediatric Rheumatology

With an incidence of approximately 1:1000 children and adolescents under the age of 16, juvenile idiopathic arthritis (JIA) is by far the most common disease group in pediatric rheumatology [1]. The predominant disease manifestations are around the peripheral joints and entheses, and musculoskeletal ultrasound (MSUS) is therefore a suitable method for diagnosis and monitoring of disease activity [2]. Articular and entheseal manifestations of connective tissue diseases (mainly in systemic lupus erythematosus and mixed connective tissue disease) are also accessible by MSUS whereas the assessment of muscle (dermatomyositis) as well as skin and subcutaneous tissues (scleroderma) is still in an early research stage and will not be discussed in this review.

The Need for Objective Measures of Disease Activity in Pediatric Rheumatology

JIA is a potentially debilitating, chronic disease which affects children and adolescents of all ages, but has an overall peak incidence around 2 years of age [1]. It is divided into several subgroups with some subgroups (oligoarticular JIA) affecting predominantly large joints, specifically the knee as the most commonly affected one followed by the ankle and wrist, whereas in polyarticular JIA, the small joints are also affected in a higher percentage [2]. Dactylitis as a specific type of involvement of the fingers can be found in oligoarticular JIA as well as the subgroup of psoriatic arthritis. Finally, the enthesitis-related arthritis subgroup of JIA is characterized by involvement of peripheral entheses in addition to synovitis. The involvement of the axial skeleton is much less frequent in children and tends to occur more often in adolescents presenting with the disease.

Treatment options have evolved dramatically over the past two decades, and it has become clear that appropriate

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guidance of these treatments is necessary in order to apply them optimally and improve outcomes [3]. As recently as 10 years ago, the evidence base for the use of pediatric MSUS was almost non-existent, but this has changed dramatically since [4]. Recent advances in sonography have stimulated the increased use of this modality in the assessment of pediatric joint disease [5–9]. Sonography is ideal for assessing the pediatric musculoskeletal system, largely because of its ability to visualize the various periarticular and intraarticular structures including cartilage and bone without the need for radiation. This is especially relevant in light of the young age at which many of the patients present, making the clinical assessment and history less reliable and favoring imaging techniques that do not require sedation. Sonography is very sensitive in detecting synovitis, tenosynovitis, paratenonitis, and enthesitis. Multiple joints can be assessed at the same time and even very young children can be examined without sedation. It can also be used to guide joint aspirations or injections [5–9].

Building the Evidence Base for the Use of MSUS in Pediatric Rheumatology

The two dominant areas of research in the past 5 years have been the standardization in the sonographic assessment of the pediatric joint and the distinction of pathologic findings from normal sonographic anatomy.

Normal Sonoanatomy

Bones usually serve as a reference point in musculoskeletal sonography. Whereas the skeleton of an adult is completely ossified except for the articular cartilage, a varying degree of hyaline cartilage and, in some locations, fibrocartilage, is present in addition to articular cartilage in children [5–9]. The degree of ossification increases with age but varies significantly within the same age group according to the individual stage of maturation (pubertal stages). Children of the same chronologic age may be at different stages of skeletal maturation and therefore display different degrees of ossification. MSUS can distinguish well between cartilage and other soft tissue structures, but the examiner has to be aware that in a child anechoic or hypoechoic, cartilage will define the bone contour in a joint as opposed to the hyperechoic outline of the fully ossified bone seen in adults. A careful scanning technique is essential to ensure the clear differentiation of cartilage from the possible presence of fluid in the joint which would also appear anechoic or hypoechoic.

The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Ultrasound Group has therefore focused its initial work on the description of the sonographic findings in healthy children [10••]. The definitions for the sonographic appearance of the normal joint include the description of the joint capsule and the growth-plate, which is seen as an anechoic or hypoechoic line separating the epiphysis from the meta/diaphysis [10••]. The cartilage itself may display hyperechogenic spots which represent vascular channels. These are physiologic in children and should not be interpreted as pathologic [10••]. The intraarticular fat and physiologic blood flow within the joint have also been described [11].

For the differentiation of synovitis from physiologic findings, the degree of distension of a synovial recess may also be interesting as variable amounts of fluid can be found in the joints of healthy children as well. This has led to the publication of normative data for various joints [12•, 13•, 14, 15, 16•, 17•, 18•]. It has to be noted though that the definition of absolute cutoffs can be difficult, and the measurement of a distension of a synovial recess is prone to errors related to joint position, transducer pressure, the precise location of measurement, and others. They should therefore serve as a guidance really, and the longitudinal assessment in an individual patient may be more important than decisions based on comparison with normative data at a given time point. Having said this, these normative data clearly help in the distinction between physiologic and pathologic findings, and the addition of Doppler findings will help in the identification of pathology.

The increased metabolic activity in the musculoskeletal system of children during growth coincides with increased blood flow into and within bones and joints [11]. This can be detected with Doppler sonography and must be distinguished from pathologic blood flow which is an important sign of active synovitis. A significant degree of Doppler signals can be detected within healthy pediatric joints but not within the synovial recess (which should if at all only be minimally distended in this case). In many joints, for example, the elbow, wrist, knee, or ankle, the intracapsular space includes connective tissues which are extra-synovial. Doppler signals within these tissues should not be interpreted as a sign of synovitis since they can be physiologic. The OMERACT group has addressed these aspects as well including nutrient vessels directly entering bones and thereby crossing the synovial space (feeding vessels). This physiologic Doppler flow can also be observed in the area of growth plates and epiphyseal cartilage and can be reliably imaged on sonography [19].

Cartilage Thickness

Joint damage and especially cartilage loss is one of the most important radiographic outcome measures in inflammatory arthritis. The sonographic assessment of cartilage has traditionally been done by measuring cartilage thickness, but it is not clear if this is the best method to assess cartilage damage [20, 21]. Depending on the location, the presence of irregular ossification centers in the epiphysis will result in significant challenges to obtain precise measurements in pediatrics [20].

Studies assessing cartilage thickness in healthy children have therefore resulted in very high coefficients of variation especially in the wrist, limiting the utility of cartilage thickness assessments especially in younger children [20, 21]. Instead of assessing cartilage thickness, the assessment of the cartilage surface may be an alternative, but this has not been evaluated yet in pediatric rheumatology.

Pathology—Synovitis

MSUS has an important role for early diagnosis, the detection of subclinical disease, and the reliable demonstration of remission, but it is important to recognize the pediatric specific aspects for a reliable assessment.

The OMERACT group has issued definitions for pediatric synovitis on MSUS [22••]. They emphasize the need to clearly identify the synovial recess on B-mode and differentiate this recess from other connective tissue, which might be intraarticular but extra-synovial and can mimic the presence of an abnormal synovial thickening/effusion (Table 1). Only Doppler signals within an area of synovial hypertrophy will clearly be suggestive of increased blood flow as part of the inflammatory process. This clear emphasis on the precise intrasynovial and not just intraarticular location of the Doppler signals represents an evolution of and differentiation from the existing definition in adults [22••]. It is especially important in the pediatric context with the significant presence of intraarticular but physiologic blood flow that can be depicted with Doppler ultrasonography. However, the technical limitations affecting the sensitivity of Doppler especially for large joints where the joint recess is located relatively deep should be taken into account [23•, 24]. Therefore, the OMERACT definition of an US-detected synovitis in children reflects the different anatomy of the joints by allowing the diagnosis of synovitis based on B-mode only (i.e., presence of synovial thickening and/or effusion, without Doppler signal). It also emphasizes the need to define the use of this technology in a more detailed way with variations of its use and adaptations of settings according to the different joints. The possibility of the presence of physiologic Doppler signal in any area of the joint including the synovial recess requires the sonographer to recognize and distinguish them from truly pathologic findings. For instance, feeding vessels can traverse the synovial recess but can be easily recognized by their direct trajectory into the bone/cartilage [19]. Interesting aspects that need to be clarified in future longitudinal studies are the hyperemia and therefore increased visibility of feeding vessels in states of inflammation as well as peri-synovial and even periarticular hyperemia that might be an important sign of inflammatory activity but has not been studied systematically yet. An example of findings illustrating these various aspects is shown in Fig. 1.

Table 1 Pediatric definitions of synovitis on ultrasonography

Synovitis detection by US in children includes the assessment of B-mode and Doppler mode (color or power Doppler) findings.
Synovitis can be detected on the basis of B-mode findings alone. Synovitis cannot be detected based on color/power Doppler findings alone.
B-mode findings include synovial effusion and synovial hypertrophy.
A synovial effusion is defined as an abnormal, intraarticular, anechoic, or hypoechoic material that is displaceable.
Synovial hypertrophy is defined as an abnormal, intraarticular, or hypoechoic material that is nondisplaceable. Color/power Doppler signals must be detected within synovial hypertrophy to be considered as a sign of synovitis.

Definition of synovitis in children on MSUS according to [22••]

Subclinical Disease Activity

Several studies in JIA have shown that MSUS is more sensitive than the clinical examination in the assessment of joint inflammation [25–29]. These studies typically found discrepancies in the number of active joints between the clinical exam and ultrasonography with overall 30% of joints assessed as normal on physical exam showing signs of synovitis on MSUS. They do have limitations including the lack of information on normal ultrasound anatomy in children which affects the ability to determine what should be considered pathologic. It may also be difficult to draw firm conclusions from a single cross-sectional assessment as is the case in most of these studies. In an interesting prospective trial using precise definitions of pathology 33, patients with new-onset JIA MSUS 0 & 6 months after therapy MSUS showed a strong sensitivity to change with a standardized response mean of 2.44 in B-mode and 1.23 in power Doppler ultrasound. A total of 13/20 (65.0%) joints with US abnormalities were in clinical remission, and 6/21 (28.6%) patients in the ACRp90 responder group showed persistence of synovial abnormalities on MSUS [30•]. It has been shown that these imaging abnormalities correspond to histologic findings of inflammation [31].

An initial lack of clear definitions of synovitis and misinterpretation of low-grade, likely physiologic Doppler signals might explain why some of the existing literature has yielded conflicting results including the inability of the presence of ultrasound findings to predict disease flares [32]. In contrast, a recent study on 88 patients in clinical remission in whom 44 joints were assessed clinically and with MSUS, the latter was abnormal in 20/88 (22.7%) patients at baseline [33••]. At the 4-year follow-up, 41/88 (46.6%) patients experienced a flare with 38.2% MSUS-negative and 75% MSUS-positive at baseline. MSUS abnormalities resulted in an OR of flare of $R =$ 3.8, 95% (CI 1.2 to 11.5), and the combination of B-mode and

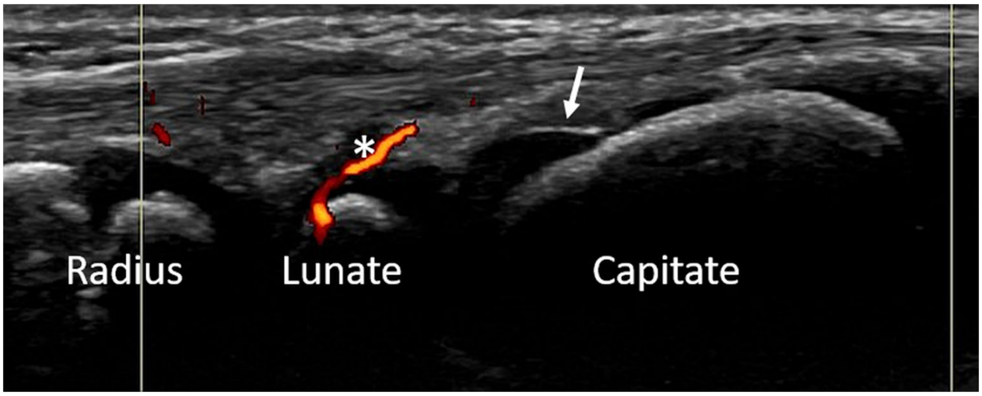

Fig. 1 Wrist joint with immature bone, small radiocarpal recess, and feeding vessel. On the proximal end (left) an interruption of the bone (radius) can be seen which represents the growth plate. A single feeding vessel can be seen passing through the mildly dilated radiocarpal joint recess (*). The cartilage interface sign is clearly visible on the proximal capitate bone (arrow) outlining the contour of the bone/cartilage clearly. The ossification of the lunate bone is also incomplete showing an anechoic halo around it

power Doppler had a higher predictive value of relapse (65%, 13/20) than B-mode alone (33%, 6/18).

Standardized Scan Positions and Quantification

Currently, only a few standard scan positions of the probe have been defined for pediatric rheumatology applications, but the range is increasing [34••, 35••, 36–38]. While the pediatric work is being completed, it is also reasonable to apply standard scanning planes that have been developed for adults to assess for pathologic findings.

The quantification of findings is another important topic both for clinical applications and research. Semiquantitative scoring systems have shown the best applicability and reliability in adult rheumatology, and they are currently being evaluated in pediatric rheumatology as well. Whereas in a clinical context, a descriptive approach, for example, “effusion in the tibiotalar joint with increased Doppler,” potentially adding measurements, may be sufficient, a gradation of findings is important when trying to assess change over time. This can be done with qualitative terms, for example, mild, moderate, and severe, but the clear definition and reliability of such terms may be a challenge. Semiquantitative scoring systems are therefore preferred. For children, several general scoring systems have been suggested, but the scoring definitions do not clearly apply to referenced illustrations in the publication itself nor do general descriptions adequately apply to all joints and all views [35••]. The development of dedicated scoring systems for individual joints may be superior to general scores for all joints. The knee joint is currently the only joint for which dedicated scoring systems are available, but only one of these systems includes the suprapatellar and the parapatellar recesses [35••]. This most recent scoring system suggesting a joint by joint approach may be an important first step towards the development of reliable scoring systems for all joints.

An important question is at which time points in the clinical course of a child ultrasonography should be used and how many joints need to be assessed. The number of joints to be scanned very much impacts the feasibility of the use of this imaging technique. In one study, a 44-joint count was compared with a 10-joint count including the bilateral knee, tibiotalar, wrist, elbow, and 2 MCP joints, and this selection was able to identify 100% of patients that did show B-mode and power Doppler findings in the more extensive 44-joint count suggesting that such a more limited joint count with an emphasis on large joints may be sufficient in JIA [34••]. The reduced number of joints was also more sensitive to change than assessing the larger number of joints [34••]. This is interesting and likely related to the fact that large joints are much more affected in pediatric rheumatology than in adults. In the reduced joint set, the large joints were overrepresented and this may have led to the better sensitivity to change.

Erosions

Ultrasound has been shown to be more sensitive than radiographs and—depending on the location and the age—equally sensitive than MRI for the demonstration of erosions in adults and children [39, 40]. Whereas bone erosions might overall be less common in JIA than RA, they still occur and are an important sign of joint damage. Few publications have studied the appearance of bone erosions in JIA with ultrasound. It does seem however that the location can be more epiphyseal than commonly in adults where the location might be more meta-epiphyseal [41]. This is likely due to the fact that the epiphyseal cartilage especially in younger children is vascularized and allows inflammatory cells and lytic factors to invade more easily and cause destruction. A recent publication has demonstrated excellent inter-observer reliability in demonstrating bone erosions in children with JIA [40].

Assessing Damage Beyond Cartilage/Bone Lesions

The radiographic assessment of joints in JIA is very much limited to the assessment of structural damage related to cartilage and bone lesions. From a functional point of view, damage to soft tissue structures may be even more important, and this would include tendon tears or partial tears, ligament lesions, and lesions to other structures supporting the normal function of the musculoskeletal system. One example would be the damage to pulleys keeping the flexor tendons of the fingers in place which may become compromised secondary to chronic inflammation with a lack of proper guidance of the tendon as a result. In the more significant cases, it will lead to so called "bow-stringing" of the flexor tendon. These aspects have not been evaluated in the pediatric literature to date.

Enthesitis

The enthesis is a relatively complex structure presenting with several components including the tendon itself, fibrocartilage, subtendinous bursae, and insertion of tendon fibers into bone which are well visualized with sonography [9]. Sonographic findings of enthesitis include loss of the normal fibrillar echotexture and irregular fusiform thickening of the tendon [9]. Sonography may demonstrate enthesophytes at the insertion of the Achilles tendon (distal posterior calcaneus) and erosions in a more proximal location along the posterior calcaneus, probably as a consequence of tensile and compressive forces occurring in these two locations. No pediatric internationally agreed definitions on the components of enthesitis are currently available in pediatric rheumatology. In adults, Doppler signals very close to bone cortex are thought to be very specific for spondylarthropathies, although they can be observed in activity-related injuries as well. Color Doppler sonography shows increased vascularity at the cortical bone insertion of the tendon and in the adjacent synovium in children with enthesitis-related arthritis (ERA) [42•]. Doppler documents increased activity at more entheses than can be shown by clinical examination in children with ERA [42•]. The clinical significance of these findings is not entirely clear. Doppler signals close to the bone cortex can be normal in certain entheseal sites in children, and different entheses may display a variable degree of physiologic Doppler signals [43•]. Knowledge of the sonographic findings in the normal enthesis is therefore important to distinguish them from pathology. Of note, the Doppler findings in the normal entheses were always on the background of a normal structure of the enthesis on B-mode. This may suggest that the combination of abnormal B-mode findings and Doppler signals may be more specific for truly pathologic findings [43•]. Sonography can also demonstrate tendon damage in addition to bony changes in enthesitis due to its superior spatial resolution.

Joint Injections

Ultrasonography is an excellent technique to both determine the affected tissues exactly and guide the needle precisely into the target. Rooney et al. described ultrasound findings in clinically swollen ankles of JIA patients. Up to 50% of children presented with tenosynovitis only and no involvement of the tibiotalar or subtalar joints [44]. This illustrates the importance of identifying the target for injections and may explain the much higher relapse rate post-injection of the ankle joint region compared with, for example, the knee joint [44]. In addition to the precise determination of joint involvement pre-injection, sonography facilitates reliable and precise access to almost any joint recess. Tendon sheaths can be injected without risking an intra-tendinous application of glucocorticoids, and joints like the subtalar and hip joint which are difficult to access without imaging guidance are relatively easy to inject under sonographic guidance [44–47]. The ability to document the correct deposition of the medication is an added advantage.

Summary

MSUS is an important measurement tool in the care for children with JIA. It helps to determine relevant subclinical disease activity, is applicable for most joints, is predictive of flare, and is well tolerated. It benefits on many levels including patient interaction to explain disease [48]. Given the increasing efforts to implement a treat-to-target approach in pediatric rheumatology, it may also help to precisely identify the target and complement clinical measurement tools like the JADAS.

Compliance with Ethical Standards

Conflict of Interest Dr. Roth reports receiving consultant and speakers fees from Abbvie and Novartis related to pediatric MSK ultrasound.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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