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REVIEW ARTICLE

Imaging of haemophilic arthropathy in growing joints: pitfalls in ultrasound and MRI

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The purpose of this review was to summarize the current knowledge on the utilization of magnetic resonance imaging (MRI) and ultrasound (US) for assessing arthropathy in children and adolescents with haemophilia and to recognize the limitations of each imaging modality and pitfalls in the diagnosis of soft tissue and osteochondral abnormalities. Awareness of MRI and US limitations and pitfalls in the assessment of joints in persons with haemophilia is essential for accurate diagnosis and optimal management of haemophilic arthropathy.

Keywords: children, growing joints, haemophilic arthropathy, imaging, magnetic resonance imaging, ultrasound

Introduction

Haemophilia is an X-linked recessive disease that manifests in males and results in a blood coagulation defect. The disease is caused by deficiency or malfunction of coagulation factor VIII (haemophilia A) or IX (haemophilia B). Musculoskeletal changes in persons with haemophilia A and B have similar imaging findings and are only distinguished based on laboratory studies. Recurrent joint bleeding in persons with haemophilia triggers a cascade of pathological changes that eventually cause progressive arthropathy with cartilage and bone damage. Joint involvement is seen in approximately 90% of patients with severe haemophilia and significantly contributes to the morbidity of the disease [1,2].

In haemophilic arthropathy, clinical examination offers functional assessment of the joint, while imaging-based evaluation helps in the detection, categorization and staging of soft tissue and osteochondral changes and provides an objective assessment of outcomes of treatment.

Plain X-rays, magnetic resonance imaging (MRI) and ultrasound (US) have been used in the assessment and scoring of diseased joints in persons with haemophilia [3–10]. Arnold–Hilgartner (AH) and Pettersson X-ray scores have been used for more than 30 years [4,5] and are limited to the direct assessment of bony changes. In the last decade, MRI has been widely used for imaging of haemophilic joints. Compared with radiography, MRI has higher tissue characterization capabilities, is more accurate and sensitive and is able to demonstrate alterations in soft tissue (effusion/haemarthrosis, haemosiderin deposition and synovial hypertrophy) and osteochondral (bone erosions, subchondral cysts and cartilage loss) structures of the affected joints [6–9].

The recent remarkable technical development in image processing of US has established a significant role for US in musculoskeletal imaging including haemophilic arthropathy. Due to its wide availability and low operating cost, US has attracted the interest of clinicians for point-of-care (POC) assessment of joints

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of haemophilic patients in their clinics [10–12]. Full (diagnostic) joint US refers to the use of US in radiology departments to diagnose and follow pathologic findings throughout the extent of the joint that is amenable to visualization by conventional US transducers (typical frequency range: 3.5–15 MHz) considering a 360° coverage approach. POC US refers to the use of US at the patient's bedside to facilitate diagnosis by answering a specific question (e.g. Is there evidence of recent bleeding in the joint?) thus holding potential for complementing physical examination and improving cost-effectiveness of diagnostic tests using a 'one-stop-shop' approach.

Despite the rapidly growing interest in the utilization of MRI and US in the diagnosis of haemophilic arthropathy and follow-up after treatment, there is scarce awareness among both radiologists and clinicians on the limitations and pitfalls of each imaging modality, a concern that could affect the diagnostic accuracy of the techniques and, consequently, clinical management of patients with haemophilia. This article aimed at highlighting some of these pitfalls of full joint US and MR imaging of haemophilic arthropathy.

Pathophysiology of haemophilic arthropathy

Haemophilic arthropathy is triggered by recurrent bleeding from the highly vascular synovial membrane lining the joint capsule. After each episode of bleeding, synovial neovascularization develops which increases the risk of further bleeding and contributes to the development of a 'target joint' [13–15]. A target joint is often defined as a joint in which three or more spontaneous bleeds have occurred within a consecutive 6-month period [16]. It is thought that adverse changes occur in both the synovial tissue and the articular cartilage secondary to exposure to blood and its breakdown products. Haemosiderin and iron deposition in the synovium initiate the release of proinflammatory cytokines and tumour necrosis factor which start a progressive process of synovial hypertrophy, synovitis and synovial fibrosis. These blood breakdown products are taken into the articular cartilage by synovial macrophages which inhibit proteoglycan synthesis. Iron-catalysed reactive oxygen intermediates induce chondrocyte apoptosis which results in progressive irreversible cartilage damage [15,17]. The damage of the cartilage starts the synovial inflammatory process again which in turn causes more cartilage damage. In vivo animal studies showed that immature cartilage is more susceptible to blood induced damage compared to the mature cartilage [17]. This is particularly important in haemophilic arthropathy as it may start manifesting in young children. Early in the course of the disease, hyperaemia from haemarthrosis and synovitis stimulates bone growth resulting in epiphyseal enlargement and osteoporosis. Later, with chronic synovial hypertrophy and cartilage damage, bone erosions, subchondral cysts, joint space narrowing, deformity and less commonly ankylosis can occur [17,18].

Scoring of haemophilic arthropathy

Clinical- and imaging-based scoring is needed to assess the condition of joints, to monitor the progression of arthropathy and to determine the effectiveness of therapeutic interventions. Commonly used clinical examination tools for assessment of joints of patients with haemophilia include the Hemophilia Joint Health Score (HJHS) and the Functional Independence Score in Hemophilia (FISH). The HJHS is performed by a trained healthcare professional, generally a physical therapist, who grades joint swelling, swelling duration, muscle atrophy, axial alignment, crepitus on motion, flexion loss, extension loss, instability, joint pain, strength and global gait (score 0 for normal and 148 for worst joint) [19–21]. The FISH is a performance-based tool that measures constraints in everyday life activities (e.g. sitting, getting out a chair) of patients with haemophilia [22,23].

Both the Pettersson (additive system based on the summation of scores related to all findings in the index joint) and the Arnold–Hilgartner (AH) (progressive system based on scoring of worst findings in the index joint) scales have limitations related to their inability to detect soft tissue pathological changes in haemophilic arthropathy, specifically regarding the detection and scoring of haemarthrosis, haemosiderin deposition and synovial hypertrophy [4,5,24,25].

In the last 15 years, several MR-based scoring systems have been proposed [7,26–30]. MRI can depict both soft tissue and osteochondral changes in reproducible and measurable ways that allow proper follow-up, and is considered the reference standard imaging technique for assessment of haemophilic arthropathy [31]. First-generation scores include the Denver [26] and the European [27] score. A second-generation score based on the Denver and European scores is the Compatible MRI scale [28]. A third-generation score which evolved from the Compatible score is the International Prophylaxis Study Group (IPSG) MRI scale [7] which is currently widely accepted by the haemophilia scientific community.

Many US scoring systems for assessment of haemophilic arthropathy have been developed (Klukowska 2011 [32]; Melchiorre 2011 [33]; Muca-Perja 2012 [34]; Martinoli 2013] [11]; Doria 2015 [35]. Recently, a proposed US-based imaging scale [0–14 scores) was adjusted to the subscores of the IPSG MRI scale (0–17 scores) [35]. To enable correspondence between US and IPSG MRI scores, items that require assessment of the entire articular surface, which is technically not feasible by US due to limited penetration of the US beam with high-frequency transducers, have been

excluded from the US scale. Excluded items are surface erosions (one item), subchondral cysts (one item) and full thickness loss of joint cartilage in at least half of the joint surface (one item).

The proposed new US scale adjusted for IPSG MRI scale [35] reports 1 as the maximum score for the finding of subchondral cysts, considering that discrimination between subchondral cysts and bone erosions is challenging on US. Nevertheless, one should consider the possibility that subchondral cysts are seen at the periphery of more than one bone which would yield an extra score of 0.5 for the item that refers to 'subchondral cysts (one or more) seen in more than one bone or if cystic changes involve a third or more of the articular surface in at least one bone'. Because US is able to depict changes only across a short extent of the articular surface (in contrast to MRI which is able to detect changes across the entire articular surface), only half of one integer would be applicable for US for this item. This raises a point for considering a maximum of 14.5 instead of 14.0 for the US scale.

Concerning cartilage degeneration, US is unable to visualize most of the intra-articular cartilage, but depicts variations of cartilage thickness along the periphery of the joint and outside the articular surface [10,11,35]. Note should be made, however, that whereas US enables visualization of the extra-articular component of the cartilage (remaining epiphyseal cartilage), MRI depicts both the extra- and intra-articular components of the cartilage. This is in contrast to other items of the US and MRI scales for which there is a direct correspondence between US and MRI.

The drive for using US for assessment of joints of patients with haemophilia resides on advantages of US over MRI such as lower cost of examinations, easier access, avoidance of sedation in young children, and lack of interference of susceptibility artefacts on gradient-recalled echo (GRE) MRI sequences in joints with haemosiderin deposition. However, a unified US scoring system is yet to be standardized and validated for clinical use in patients with haemophilia.

Limitations of MRI and sources for pitfalls

Overestimation of the amount of intra-articular haemosiderin

Blood breakdown products include deoxyhaemoglobin, ferritin and haemosiderin, which have paramagnetic characteristics. They interact with the local magnetic field during MR scanning, creating local field inhomogeneities and resulting in loss of MR signal. Extracellular haemosiderin appears as dark areas on T1 and T2 MR images, a physical phenomenon that is called magnetic susceptibility effect.

The GRE pulse sequence is one of the MR pulse sequences which are sensitive to the magnetic susceptibility effect. On GRE, image contrast depends on T2* relaxation which represents the decrease in transverse magnetization of the protons caused by magnetic field inhomogeneity and spin-to-spin relaxation [36,37]. GRE pulse sequences are commonly used to detect haemorrhage, calcification and iron deposition, substances that have short T2* relaxation time. Hence, GRE is a fundamental sequence in the evaluation of haemophilic arthropathy [8,38]. Extracellular haemosiderin appears as dark black signal on GRE sequences; however, there is associated loss of signal from the adjacent structures giving rise to what is called 'blooming effect' [36,37,39]. The summation of dark signal from normal structures to that of haemosiderin can result in overestimation of measurements of haemosiderin and suboptimal or impaired visualization of synovium on GRE sequences (Fig. 1).

Other pulse sequences such as T1, T2, proton density (PD) and water-selective sequences (WATS) do not depend on T2* relaxation time and consequently can overcome the blooming artefact effect encountered on GRE-based images. As a result, they are less sensitive to small amounts of haemosiderin. A full joint MRI protocol for examination of haemophilic arthropathy includes one or more of the aforementioned sequences in addition to the basic GRE sequences to obtain accurate assessment of haemosiderin deposition and articular cartilage status, especially in cases of excessive intra-articular haemosiderin [38]. A minimum MRI protocol includes only GRE sequences in the three orthogonal planes for elbow joints and two planes (sagittal and coronal) for ankle and knee joints [8]. It is a fast scan which is an advantage particularly when examining young children and has high capability to detect small amount of intra-articular haemosiderin; however, it has the potential for inter-reader variability when it comes to applying an MR scoring system to measure pathological changes in haemophilic arthropathy [40].

Inaccurate assessment of articular cartilage: overestimation of diffuse cartilage thinning or focal defects

There is a potential pitfall diagnosis of diffuse thinning or variable degrees of defects in the articular cartilage if measured on images obtained by GRE pulse sequence as the overlying haemosiderin can generate blooming artefact thus masking the superficial part of the cartilage (Fig. 2) [7,8,29,30].

Three-dimensional (3D) gradient echo methods have the potential to acquire data with more isotropic voxel sizes, which limits partial volume artefacts and is very accurate for the detection of small cartilage defects or surface irregularities [41,42]. 3D T1 fast field echo with water excitation for cartilage imaging (WATS-c) and intermediate-weighted fat-suppressed

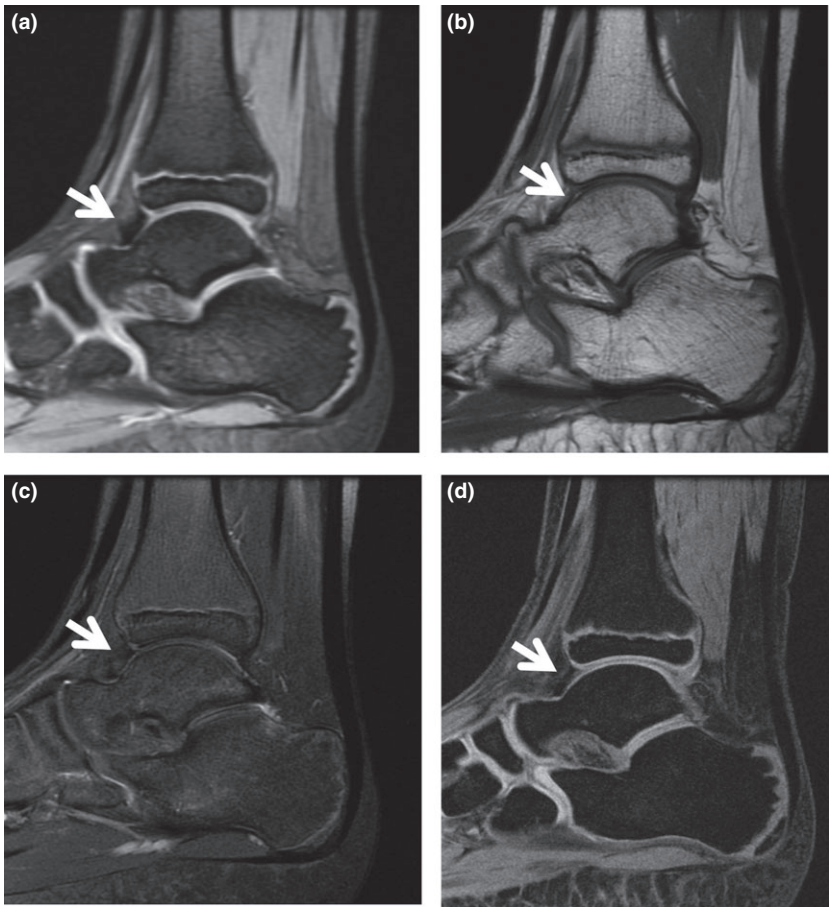

Fig. 1. Inaccurate assessment: overestimation of haemosiderin deposition on gradient-recalled echo (GRE) MR images. Twelve-year-old boy with haemophilia A and history of five previous joint bleeds in his left ankle on different pulse sequences. (a) Sagittal gradient echo (GRE) MR image shows a small dark signal haemosiderin deposit (arrow) which is less evident on (b) proton density (PD), (c) fat-saturated fast spin echo (FSE) T2 and (d) 3D fast spoiled gradient echo (FSGR) images. There is blooming artefact with GRE resulting in loss of signal from fat anterior to the joint. Measurements from this artefact can be falsely added to the real measurements of haemosiderin deposits.

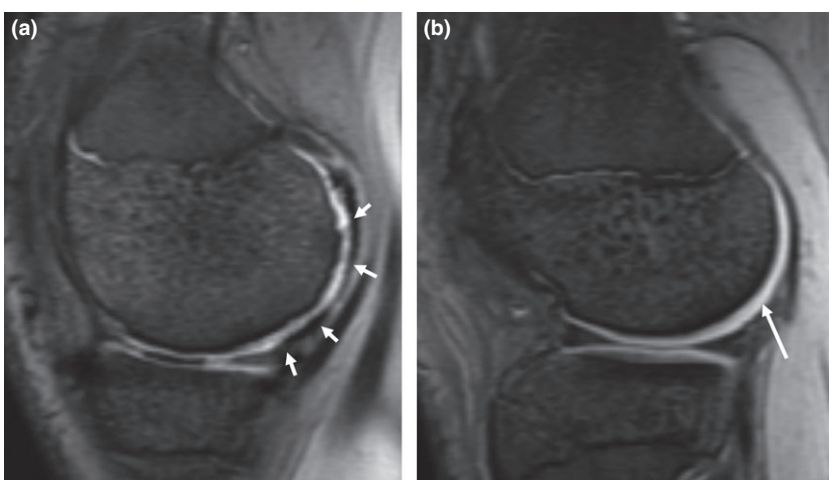

Fig. 2. Inaccurate assessment: false-positive thinning of the articular cartilage. Fifteen-year-old boy with haemophilia A and a history of 12 previous bleeds into his left knee. Sagittal multiple echo recombined gradient echo (MERGE) MR image (a) of the patient's knee shows irregular interface of cartilage (small arrows) along the posterior aspect of the medial femoral condyle simulating erosions, a pitfall because of the presence of mild haemosiderin deposits. In a fast spoiled gradient-recalled echo (FSPGR) sequence (b), normal cartilage is noted along the posterior aspect of the lateral femoral condyle, with no haemosiderin deposits evident (long arrow).

T2-weighted fast spin echo (iw-FS T2FSE) are other examples of pulse sequences that can be used to measure lesions in the articular cartilage [41].

Inaccurate measurement of the thickness of the synovium: underestimation of synovial hypertrophy

Blooming artefacts from extracellular haemosiderin on GRE MR images obscure underlying synovium in joints of patients with haemophilic arthropathy. Some investigators arbitrarily give the same grade for synovial hypertrophy and haemosiderin deposition on MRI scale (Fig. 3) [43,44]. Nevertheless, if additional MR sequences are available in the protocol [38], there is the potential for using PD sequences for scoring which should not show significant susceptibility artefacts thus enabling individual scoring for haemosiderin and synovial hypertrophy.

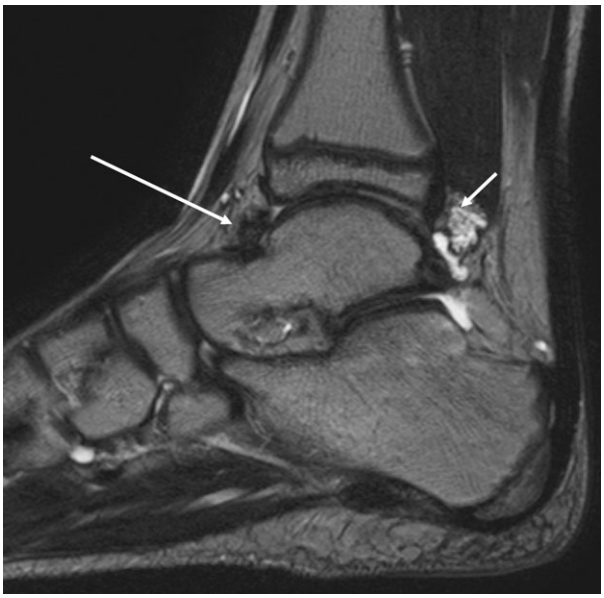

Fig. 3. Inaccurate assessment: underestimation of synovial hypertrophy upon excessive haemosiderin deposition on MRI. Eleven-year-old boy with haemophilia A and history of previous 36 bleeds in the right ankle. Sagittal fat-saturated T2 MR image of the ankle shows posterior (short arrow) hyperintense synovial hypertrophy. Anteriorly (long arrow) the dark haemosiderin deposit masks the underlying synovium, limiting measurements of the synovium thickness.

Previous investigation has shown that the use of gadolinium contrast agent is not useful for evaluating chronic haemophilic arthropathy due to the obscuration of synovial enhancement by adjacent haemosiderin deposition in cases of massive haemosiderin impregnation within the synovium [45]. In unenhanced MR studies, the low-to-intermediate T1 signal hypertrophied synovium cannot be separately discriminated from low T1 signal joint effusion or low T1, T2 or GRE signal intra-articular haemosiderin [9,31,35]. This usually results in underestimation of the degree of synovial hypertrophy on MRI. Discrimination between synovial hypertrophy and haemosiderin deposition is an advantage for US over unenhanced MR. When combined with colour Doppler, US can detect the vascular synovium in contrast to the avascular haemosiderin (Fig. 4) [46,47].

Underestimation of bone erosions

In the presence of excessive haemosiderin deposition, blooming effect can result in inaccurate assessment of bone erosions on GRE images. Underestimation of bone erosions on GRE MR images is a potential pitfall if excessive haemosiderin lies over small bone erosions concealing them (Fig. 5).

To overcome pitfalls that result from blooming artefact in MR images, it is recommended to add a pulse sequence to GRE such as WATS or PD which is less sensitive to magnetic susceptibility artefacts if quantifying haemosiderin and measuring the thickness of the synovium or the articular cartilage are required for diagnosis, treatment follow-up or scoring of joint changes cross-sectionally or longitudinally in clinical practice or research.

Limitations of US and sources for pitfalls

Technical limitations

Limited penetration power of US beam. Most of the US beam is reflected over the bony surfaces limiting the ability of US to penetrate deep joint spaces [48–50]. While marginal bone erosions, superficial subchondral cysts and peripheral articular cartilage defects can be demonstrated on US, central osteochondral changes are not accessible, especially in large joints (Fig. 6). Subchondral cysts are one of the osteochondral changes encountered in haemophilic arthropathy. They can be peripherally or centrally located in the joint and appear as rounded

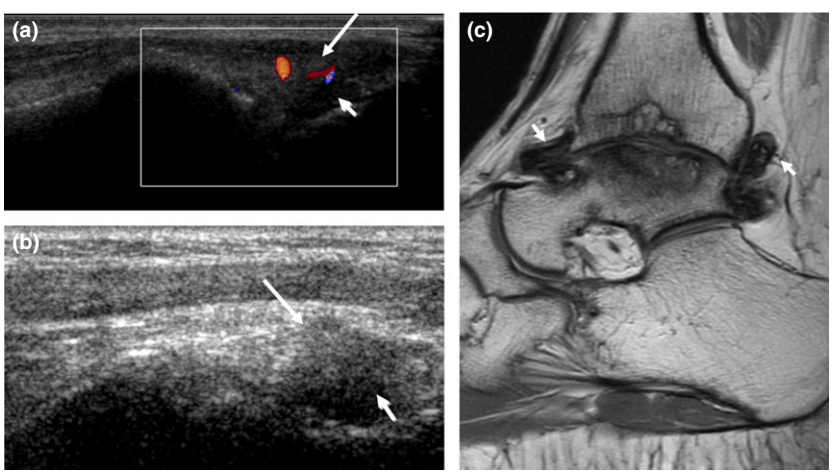

Fig. 4. Colour Doppler ultrasound (US) can help differentiating thickened synovium from haemosiderin. Fifteen-year-old boy with severe haemophilia A and a history of 61 previous bleeds into his right ankle. Sagittal L2 (joint space level) images of anterior (a) and posterior (b) aspects of the lateral tibio-talar joint demonstrate moderate echogenic synovial hypertrophy (arrows) seen on the corresponding sagittal T1 MR images (c) (arrows). Note the hypoechoic focus (short arrows in a and b) on US images corresponding to haemosiderin impregnation of the synovium. Colour Doppler in (a) shows small vessels within the haemosiderin-free/poor synovium differentiating it from areas of heavily loaded haemosiderin synovium.

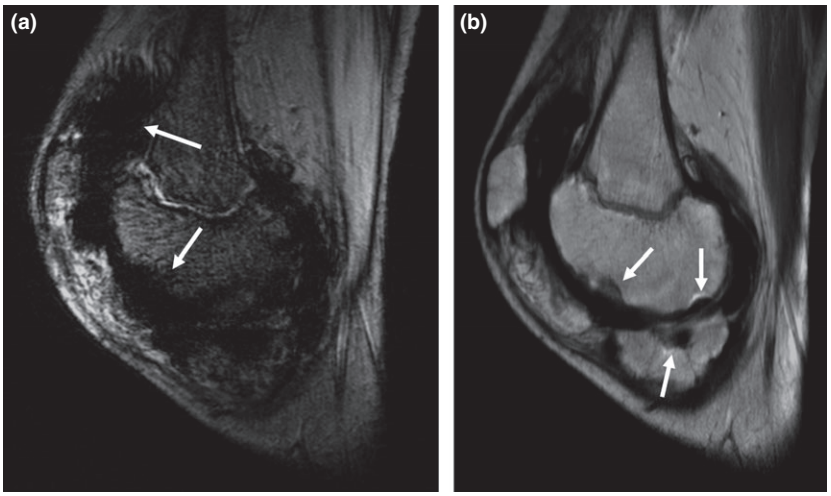

Fig. 5. Inaccurate assessment: underestimation of bone erosions on gradient-recalled echo (GRE) MRI upon excessive haemosiderin deposition. Fifteen-year-old boy with haemophilia A and history of 40 previous bleeds in his right knee. (a) Sagittal GRE MR image shows excessive dark signal haemosiderin deposits (arrows) in the medial aspect of the knee. (b) Sagittal proton density (PD) MR image reveals medial femoral condyle and upper tibial plateau bone erosions (arrows) that were concealed by blooming artefact on the corresponding GRE MR image.

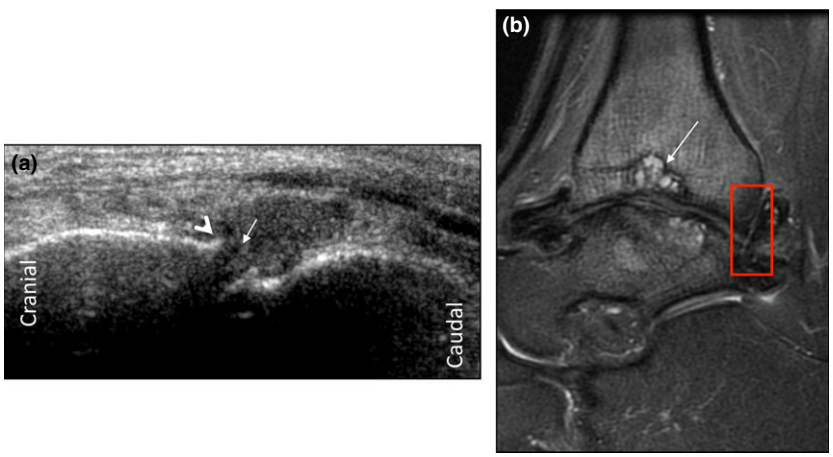

Fig. 6. False negative on ultrasound (US): inability of visualization of central osteochondral joint structures. Fifteen-year-old boy with severe haemophilia A and a history of over 60 lifetime bleeds into his right ankle. *Pitfall*: (a) Sagittal US scan of the ankle (sagittal L2 central posterior) shows low echogenicity of haemosiderin extending into the narrowed joint space (arrow) and small osteophytes in the articular surfaces (arrowhead). *Reference standard*: (b) Sagittal fat-saturated T2 MR image of same ankle shows multiple central distal tibia and proximal talus subchondral cysts (arrow in the tibia), not seen on US. Excessive haemosiderin deposits are noted within the anterior and posterior (red rectangle box) synovial recesses of the joint. [Colour figure can be viewed at wileyonlinelibrary.com]

indentations underneath the articular surface within the bone without an appreciable continuity with surface, a feature that differentiates them from bone erosions [35]. Cortical breaks may result in posterior acoustic shadowing underneath small cysts. Central subchondral cysts or large cysts extending along a third or more of the articular surface of the affected bone cannot be evaluated by US. Consequently, US tends to underestimate overall osteochondral changes in affected joints [10,35].

Technical parameters. Focal depth, choice of specific US probe and pulse repetition frequencies are adjustable factors for assessment of joints. To obtain maximum resolution, these parameters need to be properly selected to bring the surface of the target bone in the centre of the focal depth [10,35,50,51]. Adjustment of the operator setting of the US scanner is essential to clearly display the cortical bone and the overlying cartilage, and to avoid false diagnosis of bone erosions, and partial or complete cartilage loss (Figs 7 and 8). The pitfall diagnosis of cartilage defects can be generated if the US beam is not perpendicular to the surface of the bone.

The US operator should be familiar with these technical parameters, which requires adequate training in musculoskeletal US.

Challenges in the interpretation of US images

Differentiation between synovial fluid and haemosiderin. Although the ability of US to detect haemosiderin has been a controversial issue in the haemophilia imaging literature [52], we agree that the detection of periarticular haemosiderin by US is challenging and not always reliable. The detection of intra-articular haemosiderin by US is challenging. Both synovial fluid and haemosiderin appear hypoechoic on US; however, US imaging of heavily loaded synovium by haemosiderin tends to produce moderate internal echoes compared to clear synovial fluid (Fig. 9). Fluid containing particles such as those arising from recent haemarthrosis or debris from infection can produce internal echoes and is difficult to be discriminated

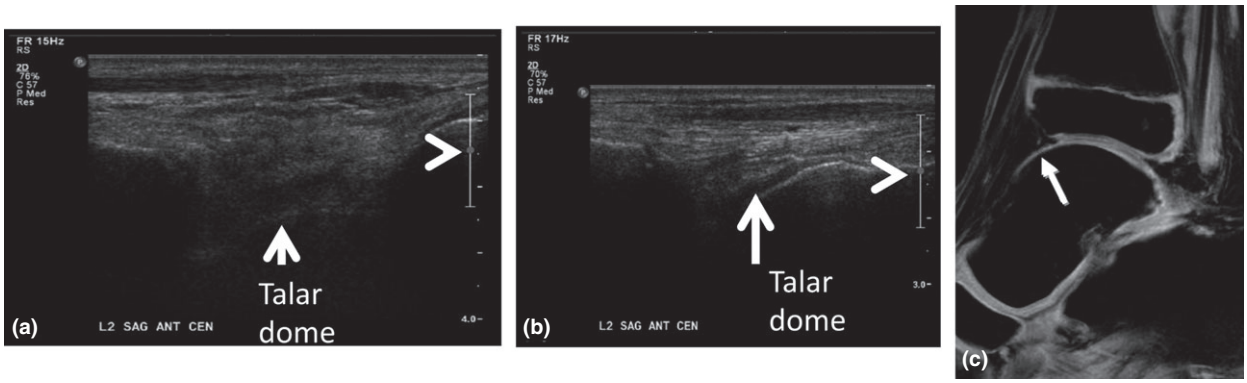

Fig. 7. False negative on ultrasound (US): operator dependency. Seven-year-old boy with haemophilia B and arthropathy in his left ankle. (a) Ultrasound image at the level of the joint line (sagittal L2 central anterior) obtained by an operator with limited US scanning experience simulates almost absent articular cartilage over the talus (short arrow). (b) Same location scanned by a more experienced operator shows intact articular cartilage (long arrow). Angle of incident US beam, repetition frequency (FR) (upper left hand corner of captions) and depth of focal zone (arrowheads) which have been adjusted to the level of the talus (arrow, in b) are factors that require training and awareness during US scanning.(c) Sagittal water-selective MR sequence of the same ankle shows intact normal thickness high signal cartilage over the talus (arrow).

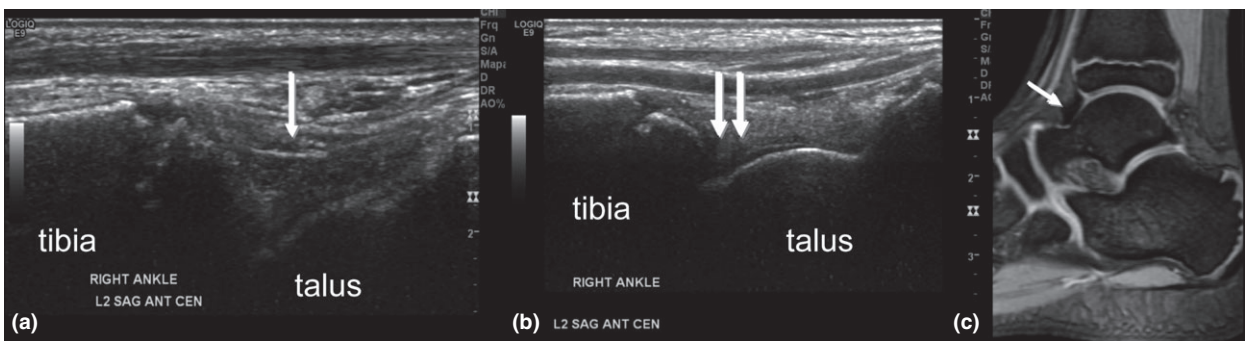

Fig. 8. False negative on ultrasound (US): technical factors. Nine-year-old boy with haemophilia A and arthropathy in his right ankle. (a) In the sagittal US scan of at the level of joint line (sagittal L2 central anterior) the anterior cortex of the talus and of the distal tibial epiphysis are not properly demonstrated. A poorly defined hypoechoic area is seen in the tibio-talar joint space (arrow) which could have represented a tiny haemosiderin deposit. Assessment of possible cartilage defects and bone erosions were suboptimum. (b) In the same plane as in (a), the depth and focal zone of caption were readjusted to lie at the level of the anterior cortex of the talus. The cortex of the distal tibial epiphysis and talar dome are now clearly identified. No erosions or cartilage defects are seen. Assessment of haemosiderin is now more accurate and appears to represent minimum deposition. (c) Corresponding gradient-recalled echo (GRE) MR image shows a small anterior haemosiderin deposit.

from haemosiderin. It is crucial to adjust the B-mode greyscale US gain when evaluating the affected joint for assessment of presence of haemosiderin. Excessive greyscale gain may increase the echogenicity of clear synovial fluid leading to a pitfall diagnosis of excessive haemosiderin [10,11,35,53].

Intra-articular haemosiderin may have the appearance of a lump within the joint space. Haemosiderin deposits may layer over the synovial lining, the articular cartilage or the intra-articular structures or along the ligaments of the joint. Haemosiderin may also be impregnated within thickened synovium [54]. There should be overall intermediate-to-low echogenicity that remains constant despite changing the patient position during the US examination to allow discrimination of haemosiderin from movable synovial fluid. Differentiation between synovial fluid and haemosiderin is more accurate on MRI where synovial fluid typically displays clear high T2 signal compared to dark signal from haemosiderin on GRE and T2 images. On US, haemosiderin impregnated within the hypertrophied synovium could be underestimated being considered as thickened synovium (Fig. 10).

Differentiation between synovium and periarticular fat. Synovium and periarticular normal fat can yield comparable intermediate-to-slightly increased echogenicity on greyscale US [54]. The discrimination between both entities on US can be challenging if they are in close proximity such as in the posterior aspect of the ankle joint (Fig. 11). Nevertheless, different groups of investigators have claimed that US is able to discriminate the moderately echogenic synovium from the hypoechoic haemosiderin [33, 35].

Evaluation of the peripheral articular cartilage and bone erosions. Studies on the diagnostic performance

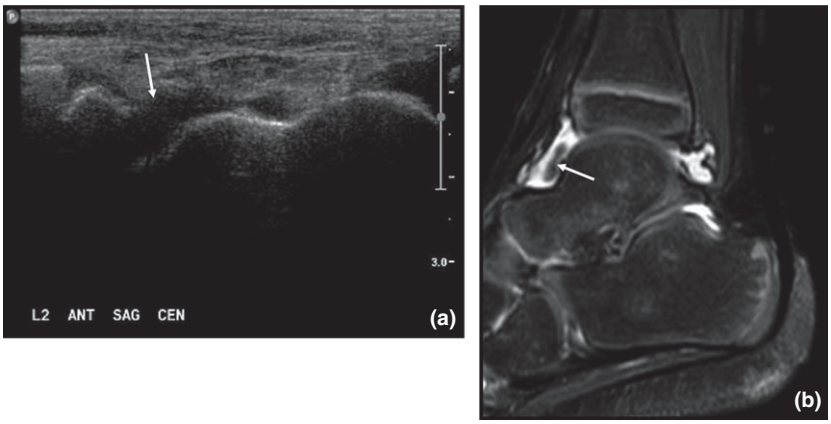

Fig. 9. False negative on ultrasound (US): inability of discrimination between synovial fluid and haemosiderin due to silhouetting effect. Ten-year-old boy with haemophilia A and history of several previous bleeds into his right ankle. *Pitfall*: (a) Sagittal US image of the patient's ankle (sagittal L2 central anterior) shows a small hypoechoic formation anteriorly in the joint space deemed by the operator to represent synovial fluid (arrow). Based on its low echogenicity and compressibility, associated haemosiderin could not be differentiated. *Reference standard*: (b) Sagittal gradient-recalled echo (GRE) MR image of the corresponding area demonstrates combined high T2 signal synovial fluid surrounding dark T2 signal haemosiderin (arrow). Whereas US could not distinguish haemosiderin from fluid as both appeared hypoechoic, MRI could.

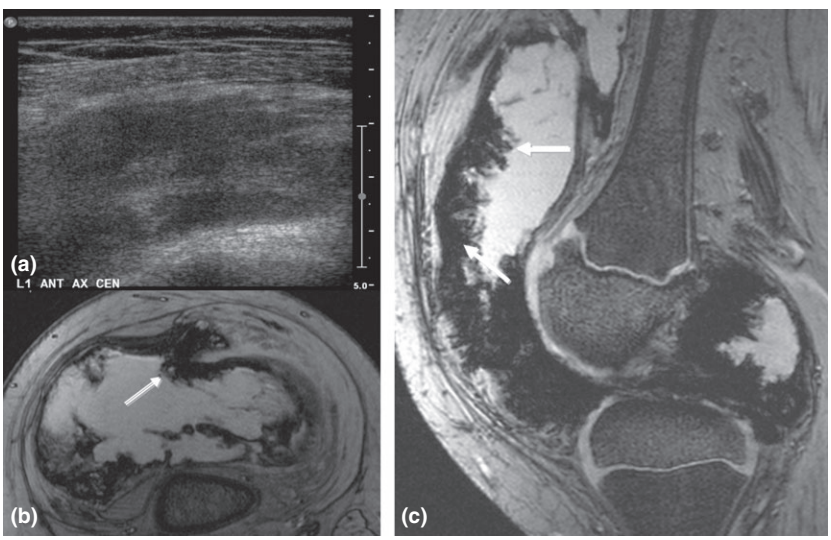

Fig. 10. False negative on ultrasound (US): underestimation of haemosiderin deposition. Eight-year-old boy with haemophilia A and a history of over 44 lifetime bleeds into his right knee. *Pitfall*: (a) Axial US image at the suprapatellar pouch (axial L1 central) shows hypoechoic joint effusion and moderately echogenic hypertrophied synovium. (L1 sagittal central anterior) shows synovial hypertrophy with villous pattern and joint fluid. *Reference standard*: (b, c) axial and sagittal MRI gradient echo (GRE) images of the knee at the suprapatellar pouch of the corresponding area show dark signal large villous synovial hypertrophy stained with speckles of haemosiderin impregnation (arrows). In the corresponding image of US, it is challenging to identify those haemosiderin deposits in the synovium resulting in underestimation of amount of haemosiderin deposition on US. On the corresponding MR images, the dark signal from excessive haemosiderin deposition is clearly depicted.

of US with regard to degenerative changes of the articular cartilage in osteoarthritis of large joints such as the knee have shown that US is a reliable indicator of cartilage degeneration when positive findings such as cartilage thinning or partial or complete loss are encountered. However, in this study a negative US examination did not rule out cartilage lesions [55]. Similar results are expected in haemophilic arthropathy.

In haemophilic arthropathy, the presence of osteochondral changes might be more extensive compared to the soft tissue changes as cartilage damage can progress without significant haemosiderin deposition or evident synovial hypertrophy [8].

The heterogeneity of vulnerability of joints to intra-articular blood damage [17] and consequent variability in image findings need to be considered. As previously demonstrated in clinical trials of different prophylaxis regimens [8,56], some patients with severe haemophilia and no prior clinically recognizable haemarthrosis develop clinically relevant arthropathy, while others with multiple clinically evident joint haemarthroses do not manifest arthropathy [Fig. 12].

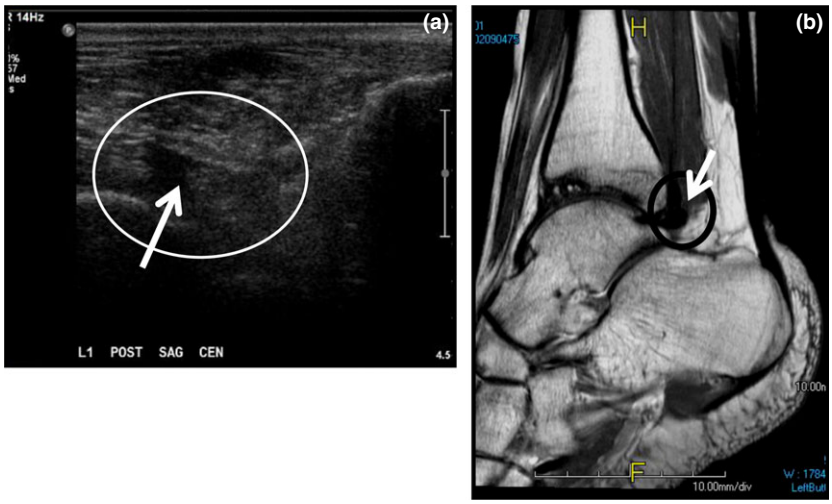

Fig. 11. False positive on ultrasound (US): inaccurate interpretation of areas of echogenicity higher than that of adjacent haemosiderin deposition mistakenly considered as synovial hypertrophy instead of soft tissue fat. Sixteen-year-old boy with severe haemophilia A and recurrent left ankle bleeds. *Pitfall*: (a) Sagittal US scan at the posterior aspect of the ankle joint (sagittal L1 central posterior) shows hypoechoic haemosiderin impregnation (arrow) and potential hypertrophied synovium with higher echogenicity in relation to the adjacent haemosiderin (circle). *Reference standard*: (b) Sagittal proton density (PD) MR image of the same area displayed on US revealed an area of dark signal representing haemosiderin deposition (arrow), normal posterior periarticular fat (circle), and lack of evidence of synovial hypertrophy. [Colour figure can be viewed at wileyonlinelibrary.com]

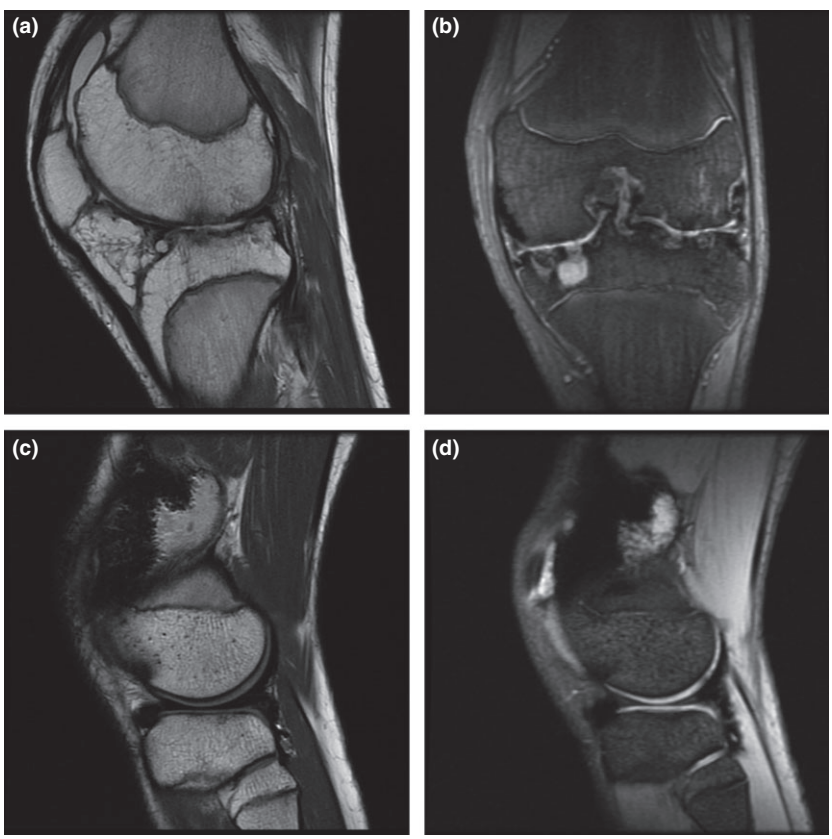

Fig. 12. Heterogeneity of manifestation of haemophilic arthropathy in a given joint according to evidence of prior local haemarthrosis due to inherent biological diversity. Left knee (a, b) of a 15-year-old boy and right knee (c, d) of a 16-year-old boy, both with haemophilia A and with histories of 18 and 25 lifetime bleeds into their knees, respectively. Sagittal proton density (PD) (a) and coronal fat-saturated fast spin echo T2 (b) MR images of the left knee show marked erosions, subchondral cysts and only minimal haemosiderin deposition from previous joint bleeds. Sagittal proton density (c) and fat-saturated T2 (d) MR image shows marked haemosiderin impregnated into synovial villosities; however, the cartilage of the lateral femoral condyle and proximal tibia appear intact.

The limited access of US to the central parts of the joints particularly in large joints which are commonly involved in haemophilic arthropathy makes evaluation of the entire area of the articular cartilage incomplete [35]. The low-to-intermediate echogenicities of the intra-articular haemosiderin in relation to the adjacent musculature may conceal the underlying cartilage as both appear as hypoechoic structures leading to a silhouetting effect which results in a false diagnosis of cartilage defect or in an inaccurate assumption of intact cartilage (Fig. 13). Keeping the US beam perpendicular to the surface of the bone whenever measuring the thickness of the intra- or extra-articular cartilage is required to avoid overshortening of the cartilage thickness and a pitfall diagnosis of cartilage thinning when normal cartilage thickness is present.

Bone erosions appear as focal interruptions of the echogenic line that represents bone cortex. Whereas high-resolution US is highly sensitive to detect bone erosions compared to X-ray and reasonably sensitive

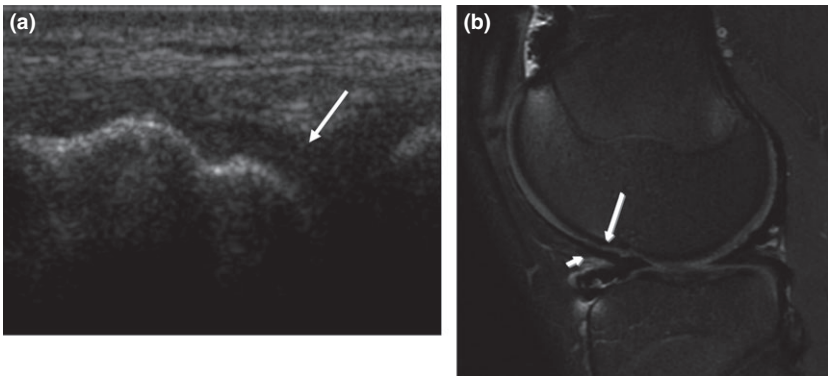

Fig. 13. False negative on ultrasound (US): underestimation of peripheral cartilage abnormalities due to silhouetting effect from underlying haemosiderin. Sixteen-year-old boy with severe haemophilia A and a history of over 20 lifetime bleeds into his right knee. *Pitfall*: (a) Sagittal US scan of the right knee (L2 sagittal central anterior) shows hypoechoic haemosiderin and undifferentiated joint cartilage (silhouetting effect). *Reference standard*: (b) Sagittal MR gradient recall echo (GRE) image shows a slightly reduced thickness of the high signal cartilage (long arrow) differentiated from the overlying dark signal haemosiderin deposits (short arrow).

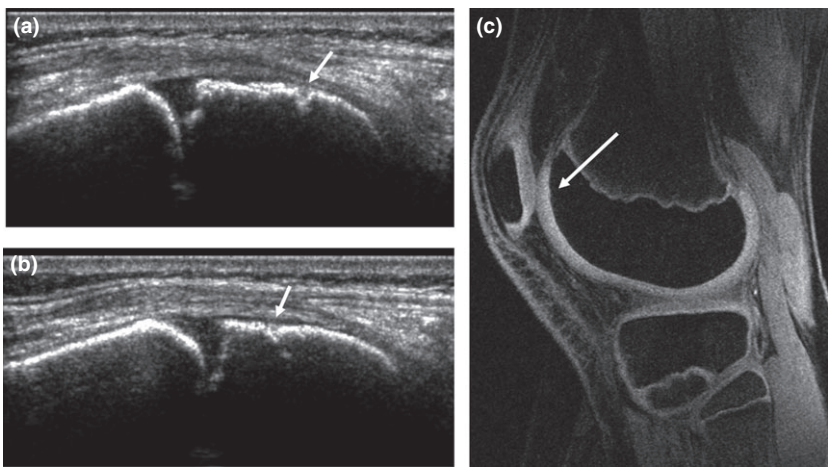

Fig. 14. False positive bone erosions by ultrasound (US). Eleven-year-old boy with severe haemophilia A and no history of previous bleeds into his left knee. Sagittal US scans of the patient's left knee (sagittal L1 lateral anterior) (a, b) show small erosions on the anterior aspect of the lateral condyle (short arrows). Sagittal multiple echo recombined gradient echo (MERGE) MR image (c) of the corresponding area demonstrates no erosions, just a small normal irregularity of subchondral bone (long arrow), a pitfall on the corresponding US images.

Table 1. Summary of MRI and ultrasound (US) pitfalls in haemophilic arthropathy with source of pitfall and suggested management.

Pitfalls	Source of pitfall	Suggested management
MRI		
Overestimation of haemosiderin deposition on gradient-recalled echo (GRE) MR images Overestimation of cartilage thinning or focal defects Underestimation of bone erosions on GRE images if excessive haemosiderin is present Underestimation of synovial hypertrophy in presence of excessive haemosiderin	Blooming artefact on GRE images	Adding pulse sequences that are not dependent on T2* relaxation time (e.g. proton density and fat-saturated T2) 3D isotropic imaging reduces partial volume averaging artefact and allows for detection of small cartilage defects and bone erosions
US		
Technical factors can result in false negative or false positive diagnosis	Improper selected frequency Inadequately adjusted focal depth Inappropriate increased or decreased US gain Suboptimum scanning technique	Optimizing operation settings particularly focal depth and selected frequency, and careful scanning with US beam as perpendicular as possible to the examined surface
False negatives of US		
Inability of discrimination between synovial fluid and haemosiderin	Silhouetting effect between materials of comparable echogenicities (both fluid and haemosiderin are hypoechoic)	Adjusting US gain to a threshold level that can detect internal echoes in haemosiderin Changes in the position of the patient's joint can mobilize joint fluid
Inability of visualization of central osteochondral joint structures such as subchondral cysts, bone erosions and cartilage loss	Limited penetration power of US beam and excessive reflections from adjacent bony articular surfaces	Comparing US to other modalities that can depict central osteochondral changes such as MRI or, in advanced arthropathy, plain X-ray
Underestimation of abnormalities in the peripheral cartilage	Silhouetting effect from underlying haemosiderin; both cartilage and haemosiderin are hypoechoic	Comparing US with MRI in equivocal cases

Table 1. (Continued)

Pitfalls	Source of pitfall	Suggested management
False positives of US		
Inaccurate interpretation of areas of echogenicity higher than that of adjacent haemosiderin deposition mistakenly considered as synovial hypertrophy instead of soft tissue fat	Comparable increased echogenicity of the synovium and periarticular fat	Being aware of areas of abundant normal periarticular fat. Adding colour duplex can assist if reactive synovial vascularity is present
Inaccurate interpretation of bone erosions adjacent to the growth plate	Normal cortical irregularities and defects over normal growth plates	Being aware of normal variation and checking with the opposite joint if normal. Compare with other modalities as MRI and plain X-ray

compared to MRI especially in small joints, false-positive diagnosis of bone erosions in areas of normal developmental focal cortical irregularity in young children can occur (Fig. 14) [35].

Level of training of the operator

The experience of the operator is particularly relevant in musculoskeletal US imaging which is a subspecialized field in medical imaging where optimizing the technical parameters of scanning and acquiring/maintaining knowledge of the complex anatomy of musculoskeletal structures is crucial. Skilled US operators are of utmost importance in the assessment of haemophilic arthropathy as the interrogated pathological findings can be subtle in early disease. Implementation and standardization of the acquisition protocol with optimal anatomical planes could reduce US operator dependency in the future.

Summary and conclusions

Currently MRI is the reference standard modality in the evaluation of and scoring of haemophilic arthropathy, despite limitations for accurate quantification of haemosiderin and synovial hypertrophy given the presence of susceptibility artefacts on GRE images. US is emerging as a low-cost diagnostic tool with a growing clinical interest in POC US assessment and follow-up of patients with haemophilic arthropathy despite challenges in total joint visualization from limited tissue penetration with high-resolution probes. Thus, both MRI and US have limitations in the evaluation of the wide spectrum of pathological changes encountered in haemophilic arthropathy which require awareness to avoid false-positive or false-negative results (Table 1). Adjustment of the technical parameters and optimization of the image acquisition protocols are key factors to overcome such pitfalls. In several clinical contexts, MR and US can be complementary in the evaluation of haemophilic arthropathy, being useful to solve diagnostic dilemmas and to ensure an accurate assessment of the patients' joints.

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Author contributions

Doria A.S. and Soliman M. conceived and designed the study. Daruge P. and Soliman M. collected and archived most of the images used in the study. Daruge P., Dertkigil S.S. J., Fernandes EA., Negrao J.R., Mitraud S. A. V., Sakima E.T.I., Fernandes A.R.C. and Mohanta A. acquired, analysed and interpreted the data. Daruge P., Dertkigil S.S. J., Fernandes EA., Negrao J.R., Mitraud S. A. V., Sakima E.T.I., Fernandes A.R.C., Mohanta A., Zhang N., Huo A., Li Y.-J., Zhou F., Rodrigues B.M., Blanchette V. and Doria A.S. contributed to the observation and discussion of the various pitfalls shown in this work, critically reviewed the manuscript for important intellectual content and approved the final version for publication. Soliman M. wrote the first manuscript draft. Doria A.S. supervised Soliman M. throughout the conduct of the study and provided multiple reviews for the manuscript draft prior to final review by the other authors.

Disclosures

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