Accepted: 13 February 2018

DOI: 10.1111/hae.13449

SUPPLEMENT ARTICLE

WILEY Haemophilia

Joint disease in haemophilia: Pathophysiology, pain and imaging

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Haemarthroses cause major morbidity in patients with haemophilia. Blood has devastating effects on all joint components, resulting in synovitis, osteochondral degeneration and ultimately end-stage haemophilic arthropathy. Key players in this process are iron and inflammation. Preventing joint bleeds is of utmost importance to maintain joint health as targeted therapies directed against blood-induced inflammation and iron-mediated processes are lacking. Joint bleeds result in acute pain as well as chronic pain due to synovitis or arthropathy. Acute pain originates from nociceptors activated by tissue damage. In chronic inflammation, central and peripheral sensitization of nociceptors might occur resulting in chronic pain. This also triggers a series of brain disorders such as emotional fear, anxiety, mood depression and impairment of cognitive functions. Treatment of haemophilia-related pain not only consists of analgesics, but also of exercise, education and in selected cases antidepressants and anticonvulsants. For objective assessment of joint structural outcome and detecting earlier changes of haemophilic arthropathy, both ultrasound (US) and magnetic resonance (MR) imaging have shown valuable. Both can be considered equally able to reveal signs of disease activity. MR imaging is able to visualize haemosiderin deposition and is more comprehensive in depicting osteochondral changes. Disadvantages of MR imaging are the duration of the examination, evaluation of a single joint at a time, costs and may require sedation, and it may need intraarticular contrast injection to depict initial osteochondral changes with accuracy. As such, US is a more useful screening tool and can be used for repeated follow-up examinations.

KEYWORDS
arthropathy, haemarthrosis, imaging, pain

1 | PATHOPHYSIOLOGY OF HAEMOPHILIC ARTHROPATHY

Recurrent joint bleeds are the hallmark of severe haemophilia and may result in haemophilic arthropathy, a debilitating condition causing pain and affecting functionality, participation and as such quality of life in patients with haemophilia (PWH). Prophylactic clotting factor substitution aims at preventing bleeds and preserving musculoskeletal function. A large United States registry shows its effectiveness in reducing joint bleeding rates, but also demonstrates the importance of early initiation to preserve joint structure and function.[1] A single joint bleed can have devastating effects on all joint components.[2]

The most affected joints are the elbows, knees and ankles.[3] The predilection for bleeding into these large synovial joints is probably a consequence of the rich vascularization of synovial tissue, its exposure to intensive mechanical forces, in combination with a shifted haemostatic balance. Compared to other tissues, clot formation is already impaired in the normal joint. Its expression of tissue factor is relatively low,[4,5] whereas the level of tissue factor pathway inhibitor (TFPI) is high.[6] In addition, in the haemophilic joint, local fibrinolysis is increased.[7] After a first bleed,

synovial thickening and formation of new, brittle blood vessels increase the risk of recurrent bleeding.

The onset of joint bleeding generally occurs when children start walking (median age at time of first joint bleed 1.8 years[8]) demonstrating the importance of mechanical forces in initiating a bleed. The synovium is responsible for clearance of blood remnants including erythrocyte-derived iron from the synovial cavity. Synovial tissue of haemophilic patients seems to adapt to an increased iron processing as the expression of iron regulators is increased.[9] Nonetheless, in case of an ongoing or repeated bleed, the synovial cleaning capacity might be overwhelmed resulting in iron accumulation in the form of haemosiderin. This induces synovial changes such as inflammation,[10] hyperplasia[11,12] and angiogenesis.[13,14] In the case of a single bleed, these changes might be transient, except the vascular changes which seem irreversible.[13] Herewith, the joint is more vulnerable to repeated bleeding inducing persistent hyperplasia and inflammation, further increasing the risk of bleeding and chronic synovitis.

Cartilage damage results from a combination of direct effects of blood exposure as well as secondary effects due to synovial changes. Synovial production of pro-inflammatory cytokines and proteases causes breakdown of cartilage matrix components via an upregulation of cartilage-degrading enzymes.[10] This effect might be transient after a single bleed as the cartilage has regenerating capacity as long as the chondrocytes remain vital. However, synovial-independent effects of blood exposure on cartilage induce both extracellular matrix degradation and chondrocyte apoptosis resulting in irreversible damage.[15,16] Pro-inflammatory cytokines produced by activated monocytes/macrophages cause cartilage degradation, but also stimulate chondrocytes to produce hydrogen peroxide. Together with haem-derived iron, hydroxyl radicals are formed leading to chondrocyte apoptosis and therewith abolishing the ability to maintain and renew the extracellular matrix. In this process, a pivotal role for interleukin-1β is shown; blocking its activity can completely prevent cartilage degradation and chondrocyte apoptosis *in vitro*.[17]

Blood exposure also leads to bone changes clinically characterized by cyst formation, subchondral sclerosis, osteophyte formation, epiphyseal enlargement and osteoporosis.[18] Little is known about the exact pathophysiologic mechanisms underlying these changes. Some features might be secondary to cartilage degeneration as they resemble other degenerative diseases such as osteoarthritis (OA), although subchondral bone changes are also suggested to induce cartilage damage in OA.[19] Bone loss might be induced by a single bleed[20] and will be exaggerated by inactivity, muscle weakness and repeated bleeding. A local shift towards bone resorption in the receptor activator of nuclear factor-κB (RANK)/RANK ligand/osteoprotegerin pathway is observed in the synovium of patients with haemophilic arthropathy. This pathway is important in bone resorption induced by inflammation.[21] Subchondral bone cysts are a prominent feature in haemophilic arthropathy, but little is known about its pathophysiology. Studying its development is hampered by a lack of cyst formation in preclinical models, but recently subchondral cyst formation was identified in a haemophilia A rat model.[22] Future research is needed to elucidate the pathways involved in bone damage in haemophilic arthropathy.

Although our overall understanding of the pathophysiology of haemophilic arthropathy has increased substantially over the past decades, this has not yet resulted in targeted therapies. Prophylactic clotting factor substitution is very expensive, not ubiquitously available, and might result in inhibitor development. Even with prophylactic treatment, joint disease still occurs.[23] At present, the only therapeutic options for haemophilic arthropathy are orthopaedic surgery and conservative treatment with the aim of preservation of function and pain relief to postpone orthopaedic surgery as long as possible.

Targeted treatment options preferably are directed against iron deposition, inflammation, hyperfibrinolysis, cartilage damage and/or bone remodelling. Some of these treatments have shown beneficial effects, predominantly in a preclinical setting, but none are translated into clinical practice yet.[24] Retrospective cohort studies demonstrate potential for cyclo-oxygenase 2 inhibitors in the management of haemophilic arthropathy,[25,26] but prospective, controlled studies are not performed, and their effects on structural changes or long-term outcome are unknown. Regenerative approaches are tested in two small cohorts of haemophilia patients. In five patients, bone marrow-derived mesenchymal stem cell transplantation was combined with synovectomy and arthroscopic debridement of the ankle and use of autologous platelet-rich fibrin.[27] This resulted in an improvement in symptoms, functional ability and signs of regeneration of cartilage and bone after a mean follow-up of 2 years. Ankle joint distraction was performed in ten patients, resulting in improvement in pain, increased functionality with preservation of the ankle range of motion and structural changes on X-ray and magnetic resonance (MR) imaging (a decrease in cysts and bone marrow oedema).[28,29] Cartilage regeneration was suggested by an increase in joint space width. For all these approaches, more studies are needed to determine their position in the treatment of arthropathy.

2 | MEDICAL MANAGEMENT OF PAIN AND FUNCTION: NEUROPHYSIOLOGICAL AND PSYCHIC ASPECTS

Most PWH experience acute pain with bleeds and may suffer from chronic pain due to synovitis or arthropathy. Surveys among PWH demonstrate that pain is a substantial problem, and a relevant proportion of patients feel their pain not sufficiently treated.[30-33]

Pain management strategies for PWH suggest a stepwise approach according to a modified "pain ladder" for non-cancer pain, considering the specific risks for patients with haemophilia. Clotting factor replacement is the first step in bleeding-related acute pain. In persistent pain, as second step after paracetamol, for adults, traditional or cox 2-selective NSAIDs are recommended and gastrointestinal versus cardiovascular risk should be weighed according to comorbidities.[3,34] The third step would include strong opioids. Whenever possible, the underlying condition should be treated (eg

physiotherapy, anti-inflammatory treatment, radiosynoviorthesis, surgical interventions such as synovectomy, joint replacement or arthrodesis). Long-term analgesic treatment is limited by increased cardiovascular and/or gastrointestinal risk with NSAIDs and loss of efficacy with opioids. Knowledge about pathophysiology of chronic pain may help to implement further treatment approaches in prevention of chronicity and treatment of chronic pain in PWH.

2.1 | Neurophysiology of chronic pain

Tissue damage leads to release of prostaglandins and neuropeptides which stimulate nociceptive sensors. These nociceptive signals are transported by neural fibres to the dorsal horn of the spinal cord. From there, signals are sent to different brain regions. In the cortex, modulated by the limbic system, the pain sensation evolves. In addition, pain can be caused by lesions or by an impaired function of the nervous system itself, described as neuropathic pain.[35]

Acute pain almost always originates from nociceptors with the aim to cause reactions to prevent further tissue damage (ie withdrawal of the body part and rest). Activation of certain regions of the midbrain activates extremely powerful descending pain-modulating pathways that project to neurons in the dorsal horn controlling the ascending information in the nociceptive system (endogenous pain control).[36,37]

When nociceptors keep "firing", the dorsal horn neurons may become hypersensitive by triggering hyperexcitability of N-methyl-D-aspartate (NMDA) receptor sites of second-order neurons in the dorsal horn with reduced pain threshold and hyperalgesia, referred to as central sensitization.[36,38] In regions with chronic inflammatory activity, also peripheral sensitization of nociceptors occurs with similar, but local symptoms.[38]

Alterations in the nervous system with chronic pain are described as neuroplasticity and long-term potentiation, which may lead to peripheral or central sensitization. There are five major cortical areas that are consistently responding to acute pain: anterior cingulate cortex, insular cortex, primary and secondary somatosensory cortex and prefrontal cortex, activated by different pain stimuli, shown in human brain imaging studies.[39] It has been suggested that excitation and inhibition not only occur at the neuronal level but also at the cortical network level (ie one cortical area is activated while an adjacent area is inhibited). A disbalance in excitation and inhibition may contribute to chronic pain, and a cortical network model for chronic pain has been proposed.[39]

Unlike normal inhibitory control, in chronic pain conditions, descending modulatory influences from supraspinal structures are switched from inhibitory to facilitatory. Certain neurotransmitters play a key role in this process. Glutamate is the major fast excitatory transmitter in the anterior cingular cortex, and GABA mediates inhibitory transmission. These mechanisms explain why antidepressant and anticonvulsive comedications play a role in treatment of chronic pain.[39]

Also in PWH, peripheral or central pain sensitization has been postulated in several studies measuring pressure pain thresholds, which are reduced in PWH at site of joint affection but also at remote sites.[40-42] The role central sensitization plays in haemophilia-related pain has not sufficiently been studied so far. This mechanism might be suspected in PWH who do not respond to peripheral analgesics, that is paracetamol, NSAIDs and opioids, and should be targeted in further research.

Chronic pain also triggers a series of brain disorders such as emotional fear, anxiety, mood depression and impairment of cognitive functions. Otherwise, pain is influenced by psychological factors and behaviour.[43,44]

2.2 | Psychological factors in chronic pain

Although the dysfunctional descending pain inhibitory mechanism is primarily biological, it is influenced by inappropriate cognitions, emotions and behaviours such as catastrophizing, hypervigilance, avoidance behaviour and somatization, inhibiting endogenous pain control and promoting central sensitization.[36]

Awareness of the noxious stimulus, cognitive processing, appraisal and interpretation that leads people to act on their pain (ie their pain behaviour) are influenced by the environment (eg cultural and social values) and learning by previous experiences.[45] Beliefs, attitudes and emotions about pain are relevant factors that influence the development of chronicity. Negative thoughts and beliefs such as "hurt is harm" and "rest is best" may worsen disability and pain.[45]

2.3 | Proposed treatment approaches for PWH

As the development of central sensitization seems to be time-dependent (>3 months of noxious stimulation), early physiotherapy, for example myofascial treatment and motor control training, may prevent chronicity, with caution to avoid noxious stimulation by the procedure itself.[36] Some studies showed a hypoalgesic effect of moderate exercise and an increase in pain threshold in PWH, supporting the concept that physiotherapy and exercise may have more than local effects.[46]

Education about neurophysiology of chronic pain that aims at reconceptualizing pain probably helps to implement effective physiotherapy and exercise. To prevent chronicity and maladaptive behaviour, education should start at initial stages of pain.[36]

In chronic haemophilia-related pain, there are approaches to influence pain by enhanced self-management and behavioural and motivational changes. Pain acceptance is a key process in improved adjustment to chronic pain, which involves accepting that trying to avoid or control pain can be counterproductive and activity engagement means continuing with life activities despite pain.[47,48]

In PWH with chronic pain and suspected central sensitization, antidepressants and anticonvulsants should be considered as comedications. To shed more light on mechanisms of chronic pain in PWH and effectiveness of treatment, further research is needed.

3 | ULTRASOUND AND MR IMAGING ASSESSMENT OF HAEMOPHILIC ARTHROPATHY

Diagnostic imaging offers an objective assessment of joint structural outcome with earlier changes of haemophilic arthropathy best assessed with either ultrasound (US) or MR imaging. Both have proved able to detect and quantify the most relevant biomarkers of disease activity and degenerative damages by means of scoring scales of increasing disease severity.[49,50]

Several studies consistently showed comparable sensitivity between the two systems for detection of synovial hypertrophy.[51-53] On proton density sequences or 3D spoiled GRE, chronic synovial proliferation is characterized by intermediate intensity signal on T1- and T2-weighted sequences, a level of contrast between cartilage and fluid.[54] In the active phase of synovitis, however, the MR signal intensity from proliferating synovium may increase at such an extent to make distinction with effusion problematic.[55] The use of gadolinium-based contrast media might theoretically help differentiating active synovitis from fibrotic synovium,[56] but this would require complex techniques based on intensity-time curves and haemosiderin deposits may impair visualization of enhancement.[57] With Doppler imaging, US has proved able to detect synovial hyperaemia, defined as intrasynovial detection of blood flow signals.[58-60] In other chronic inflammatory disorders such as rheumatoid arthritis, some authors suggested the use of Doppler techniques as a mean to monitor disease activity.[61] However, intrasynovial hyperaemia at Doppler imaging is uncommonly observed in haemophilic patients and, in the rare positive cases, only a few blood flow signals are visualized, suggesting mild hypervascularity that cannot be considered relevant enough to redirect treatment and patient management.[62] As demonstrated elsewhere, most slow, low volume blood flow signals in the synovium from tiny intrasynovial vasculature and capillary circulation remain beyond the threshold of sensitivity of the Doppler systems. In addition, high variability in the interpretation of Doppler images, the need for high-end machines to get better performance and high interequipment variability is expected.[63] Given these considerations, the use of Doppler imaging as a key tool to better predict the risk of haemorrhage and identify active disease seems to be problematic.

MR imaging is a sensitive technique to visualize haemosiderin deposition in a joint, especially using T2* GRE sequences.[54,57] Haemosiderin deposits are characterized by signal void secondary to magnetic susceptibility artefact.[64] When there is a significant intraarticular amount of haemosiderin, the degree of artefact may be too strong up to make interpretation of findings straightforward. In these cases, GRE sequences should be replaced with T2-weighted tSE sequences to avoid excessive overwriting of signal void on the joint structures.[49] At US, some distinctive features between haemosiderin and synovium have been described in the literature, assuming that the first is collected free in hypoechoic pockets, has irregular contour, is less displaceable and compressible than fluid, whereas the latter is non-displaceable, poorly compressible and hyperechoic in relation to fluid.[52,60,65] These statements, however, do not appear substantiated enough and are contradicted by the evidence that haemosiderin is embedded within the synovium and cannot be found into the joint cavity as inert matter.[66] In addition, other authors did not find any difference between the US appearance of haemosiderin-laden and haemosiderin-free synovium.[63]

Regarding osteochondral surfaces, MR imaging has proved to be more sensitive in detecting early degenerative changes related to arthropathy than physical examination and radiography.[67] This technique is also able to reveal more profound disease than radiography does in the advanced stages of the disease.[68] Detailed imaging of the articular cartilage obtained with either a proton density fat-suppressed or volumetric GRE sequences may demonstrate focal and diffuse cartilage losses, whereas subchondral oedema and cysts may be associated with high-intensity signal on fluid-sensitive sequences.[49] On the other hand, US cannot provide a comprehensive evaluation of the cartilage and subchondral bone, especially at the level of the weight-bearing areas, due to problem of access of the US beam. Medullary bone changes and subchondral cysts are not revealed with this technique. Owing to the diffuse osteochondral involvement of the disease, however, such a limited evaluation does not seem impacting significantly on the sensitivity of the method to detect the occurrence and assess the severity of haemophilic arthropathy. If we refer to the osteochondral surfaces that are exposed to the US beam, this technique has proved able to detect subtle echotextural changes, partial thickness losses through extensive cartilage derangement with spatial resolution even higher than surface-coiled MR imaging.

Compared to US, MR imaging can be considered equally able to reveal signs of disease activity and superior to offer a comprehensive evaluation of the joint surfaces. Nevertheless, it cannot evaluate more than one joint in a single study, the examination time is at least 30 minutes per joint to have accurate information on the status of the articular surfaces, and joint positioning in the magnet may be difficult in advanced osteoarthritis and uncomfortable for the patient. In addition, MR imaging may require sedation in children, it is a high-cost modality with long waiting lists (no time-efficient feedback), cannot be used for serial follow-up studies and may need intraarticular contrast injection to depict initial osteochondral changes with accuracy. Although often regarded as the imaging technique of choice, MR imaging does not suit to the disease characteristics and cannot be considered a real competitor of US as a screening method for multijoint assessment and repeated follow-up examinations. In our expectations, the use of US as part of routine clinical examination by haemophilia specialists would optimize the diagnostic workflow avoiding additional costs and long waiting lists of patients submitted to imaging departments.

4 | CONCLUSION

Despite increasing treatment modalities to prevent and stop joint bleeding, its consequences still have major impact on the life of PWH. Blood-induced inflammation in combination with

erythrocyte-derived iron has devastating effects on the joint. This may result in acute and chronic pain. Treatment involves a multimodal approach, focusing on physical and psychological aspects and involving a combination of pharmacotherapy, education and exercise. To objectively assess joint changes, US and MR imaging are the modalities of choice, with US being more suitable as a multijoint screening tool and MR imaging for a detailed assessment of a single joint.

ACKNOWLEDGEMENTS

C. Martinoli has received speaker's fees from Pfizer and Philips, performed consultancy for Pfizer and Philips and acted at the advisory board of Pfizer. L. van Vulpen and K. Holstein declare no interests which might be perceived as posing a conflict or bias.

DISCLOSURES

The authors have no competing interests.

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How to cite this article: van Vulpen LFD, Holstein K, Martinoli C. Joint disease in haemophilia: Pathophysiology, pain and imaging. *Haemophilia*. 2018;24(Suppl. 6):44–49. https://doi.org/10.1111/hae.13449