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Advances and challenges in hemophilic arthropathy

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ABSTRACT

Hemophilic arthropathy is a form of joint disease that develops secondary to joint bleeding and presents with synovial hypertrophy, cartilage and bony destruction. The arthropathy can develop despite clotting factor replacement and is especially disabling in the aging population. Pathobiological tissue changes are triggered by release of hemoglobin and iron deposition in the joint, but the sequence of events and the molecular mechanisms resulting in joint deterioration are incompletely understood. Treatment options other than clotting factor replacement are limited. Improvements in the treatment of hemophilia necessitate a better understanding of the processes that lead to this disabling condition and better diagnostic tools. Towards that end, studies of the molecular mechanisms leading to the arthropathy, as well as the development of sensitive imaging techniques and biomarkers are needed. These will pave the way to identify the cause of acute pain such as joint bleeding or synovitis, detect early, potentially reversible structural changes, and predict progression of disease. This review describes current imaging techniques and the development of high resolution musculoskeletal ultrasound with power Doppler to afford point-of-care diagnosis and management, the potential utility of diagnostic biomarkers, and summarizes our current knowledge of the pathobiology of hemophilic arthropathy.

1. Introduction

Patients with severe factor (F)VIII or FIX deficiency (hemophilia A or B) suffer from spontaneous joint bleeding in childhood [1] that results in "target joints", defined as joints with several consecutive bleeds within a 6-month period [2]. Target joints often progress to hemophilic arthropathy (HA) [1,2] that is characterized by joint deformities, synovial hypertrophy, and destruction of cartilage and bone. Compared to episodic treatment of joint bleeds, prophylactic clotting factor treatment can reduce joint bleeding and the development of HA dramatically [3]. There is compelling evidence that initiation of prophylaxis in early childhood (age <2) [4] and higher intensity dosing regimens have beneficial effects on joint outcomes [5]. However, HA cannot be entirely avoided with clotting factor replacement, as shown by a high percentage of adults with hemophilia from industrialized countries ($\sim$30%–50% of patients) presenting with clinical arthropathy despite access to prophylaxis since childhood [6–8]. These recent studies do not always provide detailed information regarding number of patients on uninterrupted prophylaxis, start or intensity of prophylaxis and adherence, all of which may influence joint outcomes. However, these studies do provide evidence that HA is highly prevalent in the aging population of patients with hemophilia. This is important since HA is a disabling condition that negatively impacts physical activity and quality of life [9,10]. In the last century patients died at a relatively early age and age-related comorbidities were therefore of minor interest. This has changed with the advent of virally safe clotting factor. The life span of hemophilia patients has become comparable to that of the general population [11], making diagnosis, prevention, and treatment of HA a critical focus of hemophilia care. However, few treatment options are currently available outside of clotting factor replacement, and management chiefly comprises various synovial ablation techniques [12,13] and surgical correction including joint replacement [14,15]. Preventing or slowing the arthropathy will require targeted management, which explains the growing interest in this field. Current efforts mainly focus on three major areas, which are (1) to develop sensitive joint imaging modalities to detect early changes and diagnose the etiology of acute and chronic pain, (2) to explore diagnostic and predictive biomarkers, and (3) to understand the underlying pathobiology of HA. This review summarizes the current progress in all those areas, and aims to bring this information into clinical context.

2. Novel imaging modalities

The desire to explore structural changes and disease burden of hemophilic joints dates back almost a century, when x-ray

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technology was developed and first applied for the diagnosis and staging of medical conditions [16]. From the 1960s to the 1980s, efforts focused on devising radiographic grading systems to document progression of joint disease [17]. Two main classification systems were introduced during that time, the Arnold-Hilgartner scale [18] and the Pettersson score [19]. These systems differ in several respects. Arnold-Hilgartner scoring includes soft tissue changes and is progressive, whereby the worst imaging finding dictates the stage of arthropathy. Pettersson scoring excludes soft tissue changes and is additive, whereby each abnormality is assigned points until a maximum score is reached. Based on recommendations by the World Federation of Hemophilia, Pettersson scoring has become the most widely used radiographic staging system for several reasons that include ease of administration, exclusion of soft tissue changes that cannot be reliably assessed by x-rays, and a lesser ceiling effect as encountered with the progressive scale [17]. At the time, systems such as the Pettersson score were invaluable to document beneficial long-term effects of prophylactic clotting factor treatment on joint outcomes in observational cohorts [3,20].

Since radiography captures only irreversible late-stage changes, several new scoring systems using magnetic resonance imaging (MRI) were proposed in the early 2000s [21]. MRI permits direct visualization of cartilage, soft tissue, hemosiderin deposits, joint effusions, bony cysts, osteopenia, and marrow edema, and therefore detection of early, possibly reversible pathology. The increasing adoption of prophylactic rather than episodic clotting factor treatment in children in industrialized countries [8], and the need to detect early, subtle changes to evaluate treatment efficacy in young patients anticipated to have near-normal life spans [11], spurred investigations as to which MRI scale would be most suitable. As with radiography, several progressive and additive scales were developed, and excellent reviews of their advantages, disadvantages, and accuracy to quantify pathological tissue changes are provided elsewhere [21–23]. In 2012, the International Prophylaxis Study Group merged systems into one, attempting to enable easier comparisons across studies and populations, separating soft tissue and osteochondral changes for more detailed information [24].

However, problems with MRI include the necessity to sedate children, cost, availability, and inability to frequently scan multiple joints. This prompted investigation into alternative new imaging modalities, which led to the adoption of musculoskeletal ultrasound (MSKUS) for the imaging of hemophilic joints and its recent introduction into clinical practice [25–28]. Continued innovative development and widespread utilization for HA care are expected over the next few years. Advances in ultrasound technology permit high-resolution imaging for detailed visualization of anatomy and pathology of the musculoskeletal system, including tendons, muscles, ligaments, and fluid. With high-frequency transducers, spatial compounding and power Doppler, soft tissue resolution is greater than with routine MRI [29–31]. Comparison of MSKUS to MRI in hemophilia has demonstrated reliable detection of soft tissue and osteochondral abnormalities, cartilage destruction and effusions [32–34]. MSKUS has been demonstrated to be a critical tool to differentiate if bleeding is associated with acute and/or chronic pain and to determine if sprains, tendon/ligament tears or enthesopathies contribute to pain (Fig. 1). MSKUS examination with sonopalpation is able to distinguish complex bloody from simple serous effusions with high accuracy as confirmed by needle aspiration [25,35]. In addition, power Doppler permits rapid and dynamic assessment of synovial blood flow, thereby demarcating synovitis from fluid. In contrast, conventional MRI cannot easily differentiate joint fluid from synovitis without contrast administration [36], nor can it easily distinguish bloody from non-bloody effusions (Fig. 2). The MRI signals of acute/subacute blood products in the joint have not been studied, and the diagnosis of hemarthrosis with MRI depends heavily on the clinical context.

The ability to diagnose inflammatory soft tissue changes and synovitis with power Doppler [25,26,33,35] is important in HA. As in rheumatoid arthritis (RA), synovial hypertrophy is often present and can be accompanied by synovitis characterized by increased synovial blood flow. Power Doppler is sensitive to slow blood flow in the microcirculation [37], and therefore able to quantify synovial perfusion abnormalities. In rheumatic joints, the quantification of power Doppler signals has been validated to evaluate the response to anti-inflammatory agents by comparisons with histological specimens and contrast-enhanced MRI [37]. Based on new evidence in hemophilia, positive power Doppler signals in HA are associated with vascular remodeling and joint bleeding [38], whereby bleeding risk increases significantly with increasing power Doppler signals. This observation adds a new dimension and may become an important consideration when monitoring hemophilic joints with power Doppler.

Compared with MRI, MSKUS is rapid, less costly, does not require contrast administration or sedation and is therefore an ideal point-of-care imaging modality [36,39]. Imaging with MSKUS has been validated for a wide spectrum of musculoskeletal pathology in rheumatology, orthopedics and sports medicine, and has been recommended by the American College of Rheumatology as the point-of care imaging modality to assess disease activity [40]. For hemophilia, this is of utmost importance. Rather than assuming that a painful joint represents bleeding, MSKUS can diagnose musculoskeletal conditions for which specific treatments other than clotting factor are available. MSKUS is also mobile, with a potential for use in patients' homes or workplaces, and it can monitor resolution of hemarthrosis or inflammation [27,28].

However, among the potential difficulties with ultrasound assessment of the joints are the nonvisualization of internal bone structure, bone edema, and the inability to penetrate deeper structures such as cruciate ligaments in the knee. There is no doubt that ultrasound is operator-dependent with a learning curve for the inexperienced operator [36]. However, diagnostic ultrasound is now emerging rapidly in many medical disciplines, including medical education [41]. It is expected that appropriate training will result in the prerequisite understanding of anatomy, pathology, tissue discrimination, and planes. This will enable non-radiologists to use point-of-care ultrasound to improve diagnosis and inform treatment decisions for a variety of medical conditions in the future.

In addition to the utilization of MSKUS for point-of care imaging of painful hemophilic joints, MSKUS has been proposed for scoring joint health in analogy to radiographic or MRI scales [35,42,43]. The most recently published scoring system (HEAD-US) uses several defined transducer positions to semi-quantitatively evaluate synovium, cartilage and subchondral bone on low-cost portable machines [43]. However, this scoring algorithm has not yet been validated, and while good to excellent inter- and intra-operator reliability were reported for experienced radiologists, the same has not yet been established for non-radiologists. Long-term monitoring of joint health with ultrasound holds great promise since the ease of scanning permits fast and frequent monitoring of all joints. In general, MSKUS is evolving rapidly into a promising tool to guide treatment decisions, although the impact of MSKUS-guided treatment decisions on outcomes remains to be documented in future studies.

3. Biomarkers

As defined by the US Food and Drug Administration, a biomarker can be "objectively measured and evaluated as an indicator of normal biologic process, pathogenic process, or pharmacologic response to a