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Review Article

Joint disease, the hallmark of haemophilia: What issues and challenges remain despite the development of effective therapies?

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ABSTRACT

Although effective therapies for haemophilia have been available for decades, the prevention and treatment of joint disease remain major clinical concerns for all haemophilia patients. Early identification of joint disease is vital to initiate or modify treatment, and prevent arthropathy. However, there remains a need for more sensitive and accurate methods, which may also detect improvement in patient outcome with new therapies or different prophylaxis regimens. These topics were explored at the *Ninth Zürich Haemophilia Forum*. A summary of our shared views on the limitations of current assessment methods, and the potential advantages of more recently developed tools, is provided. Ultrasonography enables more frequent routine monitoring and the early detection of joint disease. In addition, serological markers may provide suitable biomarkers of early arthropathy. To prevent arthropathy, in our opinion, prophylaxis is key to prevent joint bleeds and subsequent initiation of the 'vicious circle of joint disease'. However, issues remain, including when prophylaxis should be started, stopped, and if it is efficacious for inhibitor patients. Once joint bleeding has occurred, enhanced on-demand treatment should be considered. For more advanced stages of joint disease, the issues regarding the treatment options available are explored. Radiosynovectomy should be performed to treat chronic synovitis, and may prevent the need for elective orthopaedic surgery (EOS). Ultimately, however, EOS can be considered once all other treatment options have been explored. While, bypassing agents have facilitated the use of EOS in inhibitor patients, a multidisciplinary approach and careful surveillance is required for good patient outcome.

Contents

Abbreviations: COMP, cartilage oligomeric matrix protein; EOS, elective orthopaedic surgery; FISH, Functional Independence Score; HJHS, The Hemophilia Joint Health Score; QOL, quality of life; ROM, Range-of-motion; U-CTX-II, urinary C-terminal telopeptide of collagen type 2; USG, Ultrasonography; VEGF, vascular endothelial growth factor; WFH, World Federation of Haemophilia; MRI, magnetic resonance imaging.

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Introduction

The major treatment aim for haemophilia is to maintain joint status and prevent haemophilic arthropathy. While advances in the products and therapies available for haemophilia have resulted in improved life expectancy, quality of life (QoL) and joint function, joint disease remains a major clinical concern for patients with and without inhibitors. Many of the questions that were first asked when effective therapies were developed are still asked today, for example: what assessments should be made and how might these measures impact upon treatment?

Members of the Zürich Haemophilia Forum convened for their ninth meeting in May 2012 to discuss the issues and challenges that remain for the prevention and treatment of joint disease. This article summarises our opinions and shared clinical experiences on key topics such as the limitations of current tools, the need for accurate and sensitive methods to assess joint status to monitor treatment efficacy and issues relating to the treatment options available to halt the progression of joint disease.

Limitations of Current Methods of Assessing and Monitoring Joint Status

The early identification of joint disease is important in order to implement or modify treatment(s) and to prevent the development of arthropathy. However, current diagnostic methods may not always detect the early stages of joint damage and disease, and there remains a need for more sensitive and precise methods. More sensitive tools are also needed to enable the detection of what may be more subtle differences in patient outcome between different regimens or with new therapies.

Although useful, physical examinations alone are not sufficient to assess the clinical situation. Currently used physical examination scoring systems include the Colorado Adult Joint Assessment Scale and the World Federation of Haemophilia (WFH) physical examination score [1]. While the latter is the most commonly used, it has been concluded that the WFH physical examination score is insensitive to the earliest stages of arthropathy, and is not able to detect differences in joint status between prophylaxis regimens [2]. Hence, other tools, in addition to imaging information, are needed [3].

Two radiographic grading systems are commonly used; the modified Arnold-Hilgartner [4] and the Pettersson classification [5]. However, radiography can only identify relatively advanced joint disease and instead, magnetic resonance imaging (MRI) is considered the gold standard for the early diagnosis of haemophilic joint disease; MRI has been shown to be able to detect worsening joint disease in the absence of clinical impairment in patients on prophylaxis [6]. To increase its sensitivity, the International Haemophilia Prophylaxis Study Group created a new, simpler to apply, MRI scoring tool which included osteochondral and soft-tissue subscores [7]. Both the total score and osteochondral subscore were found to correlate with the number of haemarthroses. Further, by separating soft-tissue and osteochondral changes, this new MRI scale may be more useful for individual patient monitoring and between-group comparisons in clinical research [7]. However, a potential shortcoming of MRI is the lack of a reliable and valid correlation between MRI images and clinical joint status in real time. In addition, MRI images frequently do not correlate with clinical status [8], and it could be suggested that MRI may therefore not be the best tool to use in the follow-up of children. We suggest that further studies may be warranted on this topic.

Newer Methods to Assess Joint Status

Physical Examination and Functional Assessments

The older scores such as the Hemophilia Joint Health Score (HJHS), which document changes in particular joints, have been updated by assessments which reflect the functional limitations that joint disease may impose upon overall musculoskeletal function, and may be especially relevant in patients with significant joint damage (HJHS2) [9].

Range-of-motion (ROM) measurement is a common method for assessing joint mobility. However, to be clinically useful, it is important to take into consideration the normal range of joint ROM measurements and the impact of aging upon these measures. It is also important to acknowledge that standard ROM measures do not take into account obese and overweight patients. In terms of aging, recently ROM was re-evaluated in a normative study ($n = 674$; males and females; aged 2–69 years) using a standardised measurement. The results showed that ROM values for all joints decreased with age and differed significantly from commonly used normative values [10]. These data suggest that the revised, normative values should be used to determine whether ROM measures obtained in haemophilia are indicative of impaired joint mobility. It may also be helpful if a similar normative study be conducted in overweight and obese males without haemophilia in order to be able to better interpret the finding that lower ROM is reported in obese patients with haemophilia with a faster rate of joint mobility loss, as compared to those with a normal body weight index [11].

One limitation of ROM measures is that not all treatment centres have a suitably trained healthcare professional. In this respect, a recently reported multicentre, QoL study conducted over 2 years in the USA observed that self-reported joint pain and motion limitation were strongly correlated with clinically measured ROM scores [12]. This finding suggests that such self-reported QoL measures may be of potential benefit in assessing clinical trends over time, and may be especially useful when a physical therapist or health professional trained in ROM measurement is not available [12]. This, and additional QoL measures available, should also be used to determine whether efforts to maintain joint status are associated with improved patient QoL.

Newer tools, particularly applicable to physiotherapy and the detection of the very earliest functional effects of early stage joint disease, are computerised dynamic pedobarography [13], computerised balance testing [14] and gait analysis [3]. These approaches may provide useful information on the general status of patients and help to detect potential joint problems that may not be identified using MRI. For example, slight joint deviations in the ankle which may contribute to ankle