Understanding the pain profile in patients with haemophilia: Impaired descending pain inhibition as measured by conditioned pain modulation

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Abstract
Introduction: Haemophilic arthropathy is associated with pain that often becomes chronic, likely caused by peripheral and central mechanisms. In the field of haemophilia, to our knowledge, the role of the descending pain pathway, which can also be involved in these pain processes, has not been examined to date.

Aim: In light of the dearth of existing literature, we sought to evaluate the function of endogenous descending pain modulation in patients with haemophilia.

Methods: Thirty adult patients with moderate to severe haemophilia A or B (median [interquartile range] age 51.0 [42.0-54.0]) and 23 healthy adult controls (age 46.5 [36.8-54.3]) underwent conditioned pain modulation (CPM) in order to examine the function of endogenous pain modulation. The CPM response was determined by scoring a test stimulus (heat) alone as well as under the influence of a conditioning stimulus (cold) on the basis of a numeric rating scale (NRS) (0 = ‘no pain’ to 100 = ‘worst possible pain’).

Results: Patients with haemophilia demonstrated a statistically significant reduced CPM response when compared with the age-matched healthy controls (median [interquartile range] NRS score: patients: −10 (−17.5−[−7.5]) vs controls: −20 (−30.0−[−13.75]); P = .002). The determined difference in the CPM response between both cohorts showed a medium effect size of $r = .433$.

Conclusion: The results of this study indicate that an impaired degree of endogenous pain modulation could be present in patients with haemophilia. Therefore, the function of the descending pain pathway should be considered regarding an individual and comprehensive pain management.

Keywords
conditioned pain modulation, haemophilia, haemophilic arthropathy, pain, rare disease
INTRODUCTION

Although anti-haemophilic treatment has improved by the development of extended half-life products or non-replacement therapies over the last decade, joint bleeds still occur in patients with haemophilia (PwH) today. These instances of bleeding may lead to haemophilic arthropathy based on changes in joint function and structure caused by inflammatory processes of synovia as well as destruction of the cartilage tissue. The course of this process is associated with pain in PwH. While an acute bleeding episode results in acute pain, the individual's pain status can shift towards being recognized as a chronic pain condition, induced by haemophilic arthropathy. Recent studies pointed out that more than 85% of patients suffered from pain over a period of the last six months, and up to 89% reported that pain during the last 4 weeks interfered with activities in daily life.

In a previous study, we showed that pain, as measured by pressure pain thresholds, seems to depend upon the structural joint situation, as assessed by the joint score. In a more recent study, we extended the pain assessment using the comprehensive quantitative sensory testing protocol in order to elucidate a haemophilia-specific pain profile. In this study, the ascending pain processing system was examined using several thermal and mechanical detection and pain thresholds. Both knee joints and the dominant hand as references were tested in order to assess joint-specific as well as general changes in the somatosensory profile. Detection thresholds for thermal stimuli were altered in PwH at both knees and the hand, whereas mechanical detection thresholds and pressure pain thresholds were altered only at both knees, indicating the occurrence of peripheral alterations in pain processing as well as general changes of the somatosensory system.

These results of local and/or central changes in pain processing in PwH can be underpinned by another study conducted using the painDETECT questionnaire, which showed that nociceptive as well as neuropathic pain components are still present in PwH.

Overall, all these data demonstrate that the ascending pain processing system can be altered in PwH. Until today, however, nothing has been established about the descending pain modulation pathway in PwH. Descending pathways from the brain cells to the spinal cord modulate and can inhibit but also enhance pain processing from the brain down to the spinal cord. Kwon et al suggested that the diminished activity of these neurotransmitters in the descending inhibitory pain pathway contributes to chronic pain mechanisms.

Whether endogenous descending pain modulation plays a role in PwH is not clear, but this mechanism may represent an important factor contributing to chronic pain in these individuals. Therefore, we focused for the first time on descending pain modulation in PwH as measured by CPM.

MATERIALS AND METHODS

In order to answer the question whether PwH suffer from impaired descending pain inhibition, the following criteria were formulated. The inclusion criteria were an age of at least 18 years and moderate to severe haemophilia A or B (only for PwH). The exclusion criteria were any bleeding events within the last 2 weeks (only for PwH), surgeries within the last year before the examination date, and intake of painkillers within 24 hours prior the testing procedure. Healthy controls were additionally excluded when suffering from pain or having regularly engaged in sports activities more than two times weekly. PwH were personally recruited within the Haemophilia and Exercise Project (http://www.haemophilia-exercise.de/en), whereas controls were identified from an internal databank of our department and contacted via e-mail.

Initially, 30 PwH and 27 controls were included in this study. Due to the presence of acute or chronic pain, respectively, four controls were subsequently excluded from the study. Therefore, the results of 30 patients with severe to moderate haemophilia A or B and 23 healthy controls were finally analysed.

2.1 Conditioned pain modulation

The CPM response was evaluated by calculating the difference between the intensity of a heat pain stimulus under the influence of a cold pain stimulus (conditioning stimulus) and the same stand-alone heat pain stimulus (test stimulus) based on a single trial. Participants were instructed to rate the intensity of this test stimulus at the end of both conditions. Pain ratings were assessed by a numeric rating scale (NRS) (0 = ‘no pain’ to 100 = ‘worst possible pain’) (Figure 1). As a result, negative values denote pain inhibition whereas positive values express pain facilitation.

The heat pain stimulus was applied to the dominant forearm by a thermode using the TSA-2001 II Neurosensory Analyser (Medoc).

In order to ensure a painful heat stimulus, the temperature of such was individually determined by pretesting. Therefore, starting at 32°C, the temperature was applied to the dominant forearm and raised by 1°C per second. Participants were asked to press the button of a response unit when the heat stimulus reached a score of 60 NRS points. The mean of three consecutive measurements was used for CPM testing. Pretests were performed on the testing day with a 5-minute rest before starting the CPM assessment.
Cold pain was induced via immersion of the contralateral forearm into circulating cold water. Using a thermoregulator (TE10D; Techne) and a dip cooler (RU-200; Techne), the water temperature was maintained as constant at 7°C (Figure 2). Both PwH and controls were asked to rate also the intensity of the conditioning stimulus after 60 seconds on the NRS scale in order to verify that a painful sensation was achieved.

2.2 Joint status

Ankle, knee and elbow joints were examined bilaterally by using the physical examination instrument recommended by the Orthopaedic Advisory Committee of the World Federation of Haemophilia (WFH). The WFH physical examination instrument based on various parameters such as swelling, range of motion and muscle atrophy. The maximum score for single knee and ankle joints was 12 points, whereas a maximum of eight score points was given for the single elbow joint. In sum, the final score of each joint resulted in an overall joint score with a maximum of 64 score points, where higher scores indicated a more affected joint.

2.3 Pain assessment

The subjective pain condition was evaluated using the pain sub-score of the WFH physical examination. By doing so, each joint was given a potential score from zero (no pain) to three (severe pain) points, leading to a maximum pain score of 18 points. In addition, grading of chronic pain severity was assessed by means of the method of von Korff, where the scale reached from zero (pain-free) to grade four (high disability, severely limiting) points. The grading of chronic pain was evaluated by characteristic pain intensity (pain at the moment, worst pain and average pain within the last 4 weeks) as well as disability items (eg disability regarding social and work activities). Both scores were assessed based on patient’s self-report.

The anthropometric and joint score data of both groups are shown in Table 1. All participants’ joint situations were examined by the same experienced therapist, who performed the WFH physical examination and CPM measurements. Written informed consent was obtained from all patients prior to the start of the study, and approval from the responsible ethics committee was achieved.

2.4 Statistics

All data were presented as medians and interquartile range (IQR, 25th-75th percentile) if not otherwise specified. Due to the non-normality of data distribution, anthropometric and clinical data were analysed using the Mann-Whitney U test. Likewise, the Mann-Whitney U test was applied to compare CPM-related data between PwH and controls. In addition, the effect ( = Z/square root N) was calculated for CPM results and interpreted as follows: small ( = .1), medium ( = .3) and large ( = .5) effect. The chi-squared test was conducted for analysing the grading of severity of chronic pain. The alpha level for all tests was set at .05. All statistical analyses were performed using the Statistical Package for the Social Sciences version 24 software program (IBM Corp.).

3 RESULTS

Patients with haemophilia presented a more impaired total WFH physical examination score (median [IQR] PwH: 20 [16-29] vs controls: 8 [7-10]; P < .001) and an increased median (IQR) joint pain score (PwH: 4.0 [1.5-6.0] vs controls: 0.0 [0.0-0.0]; P < .001). Likewise, the analysis of the severity of chronic pain showed a statistically significant difference between PwH and controls (P < .001) (Table 1).
Patients with haemophilia rated the intensity of test stimulus under the stand-alone condition with (median [IQR]) 60.0 (48.8-60) NRS points, whereas the intensity under the conditioning influence was rated with a median (IQR) of 40.0 (30.0-56.3) NRS points. In contrast, the median (IQR) intensity of the stand-alone test stimulus was assessed with 60.0 (45.0-60.0) NRS points while the same stimulus under the conditioning influence was evaluated with median (IQR) 30.0 (20.0-40.0) NRS points in the control group. As a result, the median (IQR) CPM response achieved −20 (−30.0-[−13.75]) NRS points in the control group, whereas PwH showed a CPM response of −10 (−17.5-[−7.5]) points. Therefore, the PwH showed a statistically significant degree of reduced endogenous pain inhibition when compared with the controls (P = .002), with a medium effect size (r = .433) (Table 2).

Analyses of heat pain, which was individually determined and used as a test stimulus, showed no statistically significant differences between the two groups (P = .250). Further, PwH tended to rate the intensity of the conditioning stimulus higher than the control group did (median [IQR] PwH: 85.0 [62.5-90.0] vs controls: 70.0 [60.0-82.5]; P = .090) (Table 2).

4 | DISCUSSION

The results of this study showed that PwH suffered from an impaired degree of endogenous pain modulation when compared to healthy controls. Therefore, it can be suggested that the descending pain pathway plays a role in chronic pain in PwH. Due to the fact that also PwH with mild joint pain or no pain were included in this study, one might assume that the findings of an impaired CPM response in PwH would be larger when only PwH with more intensive pain would have been examined.

The findings of our previous study, which showed reduced thermal detection thresholds at affected and non-affected sites, support the conclusion that the descending pain pathway might play a role in chronic pain in PwH. At that time, we hypothesised that prolonged nociceptive input from the affected joints may lead to a reduction in the overall sensitivity to peripheral input, induced by activation of the descending inhibitory system. Because of a continuous and heightened activation level of endogenous pain inhibition, additional activation as induced by the CPM-TASK may be truncated, which leads to an inadequately response when directly challenged by this task. Based on the current and previous results, a dysfunctional endogenous pain modulation in PwH suffering from joint degeneration can be suggested and should attract our attention in the future.

Nevertheless, the detailed clinical meaning of reduced endogenous pain inhibition in the field of haemophilia should be verified by future studies. In chronic low back pain, a reduced CPM result is associated with a larger spatial extent of pain. In order to obtain significant pain relief and to also prevent our already vulnerable patients from experiencing increased and extended pain, treatment based on the presence of dysfunctional endogenous pain inhibition should be a substantial aim of individual pain management regimens. Hence, a comprehensive pain diagnostic should involve different diagnostic tools capable of assessing the entire pain processing system.

### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PwH n = 30</th>
<th>Controls n = 23</th>
<th>U</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age * (years)</td>
<td>51.0 (42.0-54.0)</td>
<td>46.5 (36.8-54.3)</td>
<td>320.500</td>
<td>.660</td>
</tr>
<tr>
<td>Height * (m)</td>
<td>1.78 (1.74-1.84)</td>
<td>1.79 (1.74-1.84)</td>
<td>339.500</td>
<td>.860</td>
</tr>
<tr>
<td>Weight * (kg)</td>
<td>84.0 (73.4-91.0)</td>
<td>84.5 (77.3-98.0)</td>
<td>379.000</td>
<td>.364</td>
</tr>
<tr>
<td>Type of haemophilia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe A: n = 25 (83.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe B: n = 3 (10%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Moderate A: n = 2 (6.6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate B: n = 1 (3.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WFH physical examination score * (0-64 points)</td>
<td>20 (16-29)</td>
<td>8 (7-10)</td>
<td>12.000</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>WFH pain score * (0-18 points)</td>
<td>4 (1.5-6.0)</td>
<td>0.0 (0.0-0.0)</td>
<td>80.500</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Severity of chronic pain * (0-4 points)</td>
<td>Grade 0: n = 5 (16.7%)</td>
<td>Grade 0: n = 23 (100%)</td>
<td>-</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Grade 1: n = 17 (56.7%)</td>
<td>Grade 1: n = 17 (56.7%)</td>
<td>Grade 1: n = 17 (56.7%)</td>
<td>-</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Grade 2: n = 5 (16.7%)</td>
<td>Grade 2: n = 5 (16.7%)</td>
<td>Grade 2: n = 5 (16.7%)</td>
<td>-</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Grade 3: n = 2 (6.7%)</td>
<td>Grade 3: n = 2 (6.7%)</td>
<td>Grade 3: n = 2 (6.7%)</td>
<td>-</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Grade 4: n = 1 (3.3%)</td>
<td>Grade 4: n = 1 (3.3%)</td>
<td>Grade 4: n = 1 (3.3%)</td>
<td>-</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note: Data are presented as median (interquartile range) or as total number (%).
Abbreviations: WFH, World Federation of Haemophilia.
*Mann-Whitney U test.
Chi-squared tests.
Grade 0 = pain-free, Grade 1 = low disability-low pain intensity, Grade 2 = low disability-high pain intensity, Grade 3 = high disability-moderately limiting, Grade 4 = high disability-severely limiting.
In patients with osteoarthritis, studies revealed that impaired descending pain inhibition is associated with higher intensities and longer duration of pain. As a consequence, one has to figure out whether higher pain intensity and a longer exposure to pain lead to decreased endogenous pain inhibition or vice versa, if dysfunctional pain inhibition is the basis of more intensive and long-lasting pain. Hereafter, the impact of different manifestations of haemophilic arthropathy on the descending pain pathway should be clarified.

Repetitive and/or intensive pain leading to pathophysiological changes of the descending pain pathway emphasizes the need to treat any pain condition as soon as possible and using all available options (e.g., physical medicine, physiotherapy, and exercise therapy). Otherwise, if impaired pain inhibition causes pain, the descending pain pathway should be directly targeted by pharmacological options. By increasing neurotransmitters like serotonin and norepinephrine, which are significantly involved in descending pain inhibition, a level of pain relief might be achieved, which was already noted in osteoarthritis studies. Based on this, the assessment of the descending pain system may lead to more concrete pharmacological options in the future.

In sum, knowledge about pain mechanisms and the influence of additionally accompanying comorbidities like depression represents the basis for achieving sufficient pain reduction. Since serotonin and noradrenaline are involved in both depression and CPM response, one might assume that psychological factors are related to the degree of CPM response. Nahman-Averbuch et al. showed in their comprehensive meta-analysis that there is no association between CPM response and the levels of anxiety, depression, and pain catastrophizing. Certainly, the authors suggested that different testing paradigms may be affected differently by psychological factors. Nevertheless, psychological treatments might be effective for reducing pain, even when delivered combined with physiotherapy for pain and disability by physiotherapists.

For the purpose of achieving sufficient individualized pain therapy, it is important to examine the pain condition in a comprehensive manner. Likewise, it is vital to raise the awareness level of each patient not only regarding the treatment of bleeding episodes but also regarding pain treatment. Likewise, in order to ensure effective pain management, the patient should be advised that it is crucial for them to report any pain at all locations to the clinician and not just limit their comments to joint pain. Likewise, the patient should not only report pain due to bleeding but also highlight constant or repetitive (chronic) pain due to flare-ups. By doing this, their pain could be managed more adequately.

Further, a realistic plan to reach goals should be formulated between the patient and the medical staff. Especially before performing joint replacement surgery, the pain-related outcomes should be estimated as accurately as possible and should be discussed with the patient. In the field of osteoarthritis, it is known that the outcome of knee replacement surgery is related to the function of the descending pain pathway. Therefore, the pain-specific outcome of PwH, who have greater risks of postoperative complications in general, should be preoperatively assessed in detail in order to balance potential surgical risks and benefits. Also, the assessment of descending pain modulation by CPM has been found to be a predictor not only for the future pain status but also for the efficacy of pharmacological as well as non-pharmacological interventions.

**5 | CONCLUSION**

In conclusion, the results of this study are collectively another piece of a puzzle showing that general alterations in pain processing are also involved in chronic pain—albeit haemophilic arthropathy...
is primarily a local process and a reason for nociceptive pain. The fact that changes in ascending as well as descending processes are meaningful in the presence of pain in PwH, underlines the fact that testing pain processing is helpful and absolutely necessary in order to uncover the cause of pain. Only existing knowledge about individual reasons of pain enables us to treat pain in PwH more precisely and may help us to avoid invalidating pain treatment for both patients as well as physicians. In the near future, this will help to find sufficient tools for the multimodal management of pain in PwH.

6 | LIMITATIONS

The impact of disease-specific parameters (eg annual [joint] bleeding rate, genesis of haemophilic arthropathy), or other influencing factors like the individual stress level or sleep disturbance were not considered in the present analysis. Therefore, further prospective studies are needed to analyse in detail whether the function of the descending pain modulation pathway in PwH depends on the number of (joint) bleedings or if there are other influencing factors, for example pain duration. Likewise, other chronic pain sources were not evaluated, which may also influence the function of the descending pain pathway.

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DISCLOSURES

The authors state that they have no interests that might be perceived as posing a conflict or bias.

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