Neuropathic pain in patients with haemophilia, that is the question

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Keywords
Haemophilia, neuropathic, nociceptive, pain

Summary
Chronic pain caused by recurrent joint bleedings affects a large number of patients with haemophilia (PwH). The basis of this pain, nociceptive or neuropathic, has not been investigated so far. In other pain-related chronic disorders such as osteoarthritis or rheumatoid arthritis, initial studies showed nociceptive but also neuropathic pain features. 137 PwH and 33 controls (C) completed the painDETECT-questionnaire (pDq), which identifies neuropathic pain components in a person’s pain profile. Based on the pDq results, a neuropathic pain component is classified as positive, negative or unclear. A positive neuropathic pain component was found in nine PwH, but not in C. In 20 PwH an unclear pDq result was observed. In comparison to C the allocation of pDq results is statistically significant (p≤0.001). Despite various pDq results in PwH and C a similar appraisal pain quality, but on a different level, was determined. Summarising the results, there is a potential risk to misunderstand underlying pain mechanisms in PwH. In chronic pain conditions based on haemophilic arthropathy, a differential diagnosis seems to be unalterable for comprehensive and individualised pain management in PwH.

Neuropathischer Schmerz bei Hämostaseologie-Patienten, das ist die Frage
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Haemophilia is an x-linked recessive coagulopathy characterised by bleeding episodes which mostly affect the ankles, knees and elbows. Recurring haemarthrosis leads to adverse changes in the synovial tissue and the articular cartilage (1, 2). Pain plays a central role in the life of patients with haemophilia (PwH) (3–5). Caused by recurrent joint bleedings acute pain conditions may shift to chronic pain due to synovitis, enhanced cartilage damage and bone destruction (3). Pain becomes an autonomous disorder through this shift. In contrast, the knowledge about pain in PwH is very restricted to visual analogue scales or different pain questionnaires (6).

In a previous study we have shown that pain thresholds are altered in people with haemophilia (3). We were able to determine reduced pressure pain thresholds at the knee and elbow joints of PwH in comparison to control subjects. This increased pain sensitivity is related to the severity of joint pathology. Non-joint structures like sternum and forehead showed no different pain thresholds between PwH and controls. These results were confirmed by the study of Teyssler et al. (7). They also verified reduced pain thresholds in PwH.

Currently, the cause of increased pain sensitivity cannot be answered adequately. It is assumed that an acute increase of intra-articular pressure due to acute bleeding (3) and/or synovial inflammatory changes (1) may lead to these altered pain thresholds. Pain conditions in PwH seem to be based on nociceptive pain mechanisms. Nevertheless, a neuropathic pain component in the pain profile of PwH should be taken into account, which on the one hand can occur as an autonomous mechanism and on the other hand may interact with a nociceptive component. So far, neuropathic pain as an underlying mechanism for the pain condition in PwH has not been investigated nor discussed.

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Nociceptive and neuropathic pain arise from diverse mechanisms. Nociceptive pain mechanisms are classified into nociceptive (physiologic) and inflammatory pain (pathophysiologic). While inflammatory pain is characterised by tissue damage and inflammation, neuropathic pain is induced by a dysfunction or lesion of the peripheral or central nervous system (8). In inflammatory pain, inflammatory mediators sensitize nociceptors leading to allodynia and hyperalgesia. Nociceptive pain describes a suprathreshold activation of nociceptors, i.e. the classical warning symptom. The function of both mechanisms is to protect the organism from tissue damage (9). In contrast, neuropathic pain originates from damage or dysfunction within the nervous system, which may or may not be associated with potential or actual tissue damage (10). Further, plasticity changes of the peripheral or central nervous system may lead to an irreversible, autonomous pathology (9). For the pain management in PwH it is of major importance to distinguish between nociceptive and neuropathic pain mechanisms because of different treatment interventions.

Up to now, pain caused by haemophilic arthropathy has been attributed to osteoarthritis and rheumatoid arthritis pain conditions and is managed similarly (2, 11–13). Although there are initial studies, which identified features of neuropathic pain in unspecific joint pain conditions (14), osteoarthritis (15–17) or rheumatoid arthritis (18), neuropathic pain components in PwH also have to be determined. Moreover, haemophilia’s specific comorbidities such as HIV or hepatitis already comprises the option for a neuropathic pain condition by itself (19–21).

Apart from other comprehensive neurological screening tools, the pDq is a one page patient-based questionnaire which 33 persons answered. All participants were recruited by our internal database.

The aim of this study was to detect if there is a neuropathic pain component in the pain profile of PwH. We hypothesised that non-neuropathic pain is present in PwH mainly, but that there are also patients with a neuropathic pain component.

Patients and methods

Subjects

In total, we contacted 287 persons with severe and moderate haemophilia by mail. Beside an information letter, a statement of agreement and a general questionnaire, the pDq was annexed. 137 responses including a written informed consent returned to our department. In addition 57 male control subjects without any blood coagulation or joint diseases were also contacted out of which 33 persons answered. All participants were recruited by our internal database.

This study was conducted in accordance with the principles of good clinical and ethical practice (Declaration of Helsinki).

Pain questionnaire – pDq

The pDq is a one page patient-based screening tool, which identifies neuropathic components in a person’s pain profile and has been developed by the German Research Network On Neuropathic Pain (Deutscher Forschungsverbund Neuropathischer Schmerzen, DFNS) (22). The pDq is based on characteristic clinical neuropathic symptoms and “can easily be applied fully by the patient without any prior physical examination by medical personnel” (22). The questionnaire is composed of four parts whereby three of them (part 2–4) were used for the final analysis.

In the first part, current pain rating, worst pain rating within the last four weeks and mean pain ratings within the last four weeks were gathered by a visual analogue scale ranging from 0 (no pain) to 10 (worst pain imaginable).

The second part of the pDq displayed different pictures which asked for the course of pain (e.g. persistent pain with slight fluctuations or pain attacks with pain between them). Thus, patients were able to distinguish between various pain progressions. In addition, the third part queried if the pain radiated to other regions of the body. Patients were requested to mark the main area of pain on a body image as well as the direction of pain radiation. Seven questions that concern the quality of neuropathic pain syndromes’ constitute the last pDq part (e.g. Do you have sudden pain attacks in the area of your pain, like electric shocks?). Each of the seven questions were graded from 0 (never) to 5 (very strongly). Previous answers were scored for a final screening-result also. The issue on pain-course pattern was graded from −1 to +1. In addition, score points re-

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**Tab. 1**

<table>
<thead>
<tr>
<th>parameter</th>
<th>people with haemophilia</th>
<th>control subjects</th>
<th>p =</th>
</tr>
</thead>
<tbody>
<tr>
<td>n =</td>
<td>137</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>age (years)</td>
<td>45 ± 12 (19–80)</td>
<td>46 ± 16 (22–76)</td>
<td>0.953</td>
</tr>
<tr>
<td>height (cm)</td>
<td>178 ± 7.6 (160–198)</td>
<td>179 ± 7 (163–192)</td>
<td>0.321</td>
</tr>
<tr>
<td>weight (kg)</td>
<td>82 ± 14.3 (54–130)</td>
<td>81.7 ± 13.9 (56–120)</td>
<td>0.794</td>
</tr>
</tbody>
</table>

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**Tab. 2**

<table>
<thead>
<tr>
<th>parameter</th>
<th>data</th>
<th>n =</th>
</tr>
</thead>
<tbody>
<tr>
<td>type of haemophilia</td>
<td>A</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>11</td>
</tr>
<tr>
<td>severity</td>
<td>severe</td>
<td>113</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
<td>12</td>
</tr>
<tr>
<td>HIV</td>
<td>yes</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>no</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>data unavailable</td>
<td>19</td>
</tr>
<tr>
<td>hepatitis</td>
<td>yes</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>HBV</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>HCV</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>HAV &amp; HCV</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>HBV &amp; HCV</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>HAV &amp; HBV &amp; HCV</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>unavailable</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>no</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>data unavailable</td>
<td>11</td>
</tr>
<tr>
<td>most affected joint</td>
<td>knee</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>ankle</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>elbow</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>other</td>
<td>9</td>
</tr>
<tr>
<td></td>
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<td>9</td>
</tr>
<tr>
<td></td>
<td>data unavailable</td>
<td>12</td>
</tr>
</tbody>
</table>
Regarding pain radiation, graded 0 for no radiation or +2 for radiating pain, were awarded finally (22).

Based on a score-range from 0 to 38, a neuropathic pain component was evaluated as negative (a neuropathic pain component is unlikely (<15%); score: 0 to 12), unclear (neuropathic pain component can be present; score: 13 to 18) or positive (neuropathic pain component is likely (>90%); score: 19 to 38). The pDq was evaluated in 392 patients with back pain and indicated a sensitivity of 85% and specificity of 80%. A complete description of the pDq including a score manual is published by Freynhagen et al. (22).

Statistics
Statistical analyses were performed using IBM SPSS 22 (Chicago, IL, USA) for Windows. Normal distribution of data was tested by Kolmogorov–Smirnov tests. As the data were not distributed normally, statistical group comparison between PwH and controls was done by Mann-Whitney U test for score points and by chi-square tests for the final result. The alpha level for all tests was set at $p \leq 0.05$.

Results
Anthropometric data of PwH and controls are shown (▶ Tab. 1), clinical characteristics of PwH are listed (▶ Tab. 2).

PwH attained in percentage more often an unclear or positive pDq-Result based on higher score points (PwH: 8.4 vs. controls: 4.2), as seen (▶ Tab. 3). This allocation is statistically significant for the scores ($p \leq 0.001$) as well as for the pDq-results ($p = 0.006$).

The single results of the pDq in PwH are shown (▶ Fig. 1). On the basis of this mapping the distribution of particular results became apparent. In the majority of PwH, a neuropathic pain component was unlikely. Even so some results pointed out a neuropathic or an almost neuropathic pain component.

Overall, pain ratings (1st part of pDq) via numeric pain scale were scored significantly higher in PwH as in controls when current pain (PwH: 2.5 vs. controls: 1.2) (p

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**Tab. 3**

<table>
<thead>
<tr>
<th>pDq – result</th>
<th>people with haemophilia</th>
<th>controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n =</td>
<td>137</td>
<td>33</td>
</tr>
<tr>
<td>negative</td>
<td>n = 108 / 78.8%</td>
<td>n = 32 / 97.0%</td>
</tr>
<tr>
<td>SP: 5.9 ± 3.2 (0–12)</td>
<td>SP: 3.9 ± 3.7 (0–12)</td>
<td></td>
</tr>
<tr>
<td>unclear</td>
<td>n = 20 / 14.6%</td>
<td>n = 1 / 3.0%</td>
</tr>
<tr>
<td>SP: 15.8 ± 1.8 (13–18)</td>
<td>SP: 14</td>
<td></td>
</tr>
<tr>
<td>positive</td>
<td>n = 9 / 6.6%</td>
<td>n = 0 / 0 %</td>
</tr>
<tr>
<td>SP: 23.0 ± 4.9 (19–33)</td>
<td>SP: --</td>
<td></td>
</tr>
<tr>
<td>in total</td>
<td>SP: 8.4 ± 6.1 (0–33)</td>
<td>SP: 4.2 ± 4.0 (0–14)</td>
</tr>
</tbody>
</table>

Data presented as absolute/percentage and additionally as score points (SP) mean ± standard deviation (min-max).

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In this study, we detect that a neuropathic pain component is likely in approximately seven percent of our patients and appears as frequent as in the general population in Europe (27). Furthermore, one has to consider an unclear pDq result for almost 15% of our patients where additional diagnostic measures should be realised. Therefore, there is a latent risk to estimate chronic pain in PwH by means of increased nociceptive sensitivity per se and to under-recognise neuropathic pain components. The distribution of divergent results (Fig. 1) points out the risk of misunderstanding underlying pain mechanisms and verifies a very heterogeneous pain profile in PwH. Moreover, pain mechanisms still remain unknown in 15% of the patients’ cohort. Also, these data may suggest another possibility concerning a side-by-side combination of nociceptive and neuropathic pain mechanisms. Nevertheless, the pDq provides the possibility to identify neuropathic pain mechanisms simply, but also effectively and should be included in the routine pain diagnostics in PwH.

Our findings are accompanied with recent studies, which proved that a neuropathic pain condition might also be present in osteoarthritis (15–16, 28) or rheumatoid arthritis (18). The prevalence of neuropathic pain components in osteoarthritis pain ranged from 5% (16) to 34% (15). Sim et al. found neuropathic pain mechanisms in 33% of their patients with rheumatoid arthritis and neurologic symptoms (18). However, data of PwH are still missing. To sum up, joint pain caused by haemophilia, rheumatoid arthritis or osteoarthritis, can no longer be attributed to nociceptive pain mechanisms only.

Complicated by limited evidence on pain assessment and management in PwH, an individualised pain management cannot be realised. A distinct pain diagnostic in PwH, which is still non-existent, is absolutely essential to tailor specific pain treatment based on particular pain mechanisms. According to the type of pain, non-steroidal anti-inflammatory drugs/paracetamol (inflammatory pain) or opioids, anticonvulsants and/or antidepressants (neuropathic pain) must be prescribed (27). A false pain diagnostic and subsequently an incorrect pain medication may lead to an insufficient pain treatment regime, as often described (4, 29). The development of evidence-based guidelines, as mentioned by many authors (4, 7, 24), is of utmost importance and should include specific recommendations for the treatment of neuropathic pain in PwH. Only then can it be ensured that suitable medication is used for a specific type of pain. We evaluated a small number of controls to also gain awareness about pain pattern in persons with common pain in contrast to pain modalities in PwH. Between the different pDq result-groups, a comparable pattern in the pain character could be determined. Despite similar pain experience in all scanned persons, there is a big gap with respect to the subjective prevalence of pain quality (Fig. 2).

The general questionnaire was re-examined in order to identify feasible common features in PwH with a likely neuropathic pain component. Because of small subgroup numbers, additional statistical analyses were not carried out. No PwH with a pDq-score ≥ 19 points had a total endoprostheses or synovectomy, while the occurrence of arthroscopy, bone fracture and arthrocentesis arose once. On the basis of the raw data, it seems that either accompanying diseases such as HIV, hepatitis or other diseases such as diabetes or rheumatism influence the pDq result. Thus, out of nine PwH with a likely neuropathic pain component, only one had HIV and four had hepatitis. Furthermore, the allocation of HIV and hepatitis was nearly equal with a prevalence of 11% persons who had HIV in the positive pDq result group versus 16% in the negative pDq result group. The difference of hepatitis was 2% between these two groups. However, larger surveys may verify the impact of HIV or hepatitis on neuropathic pain in PwH in more detail. In all PwH with a positive pDq result, severe haemophilia A was present. Also, attention has been paid to the age pattern of the nine PwH with a positive pDq result, but no age effect can be assumed. PwH with a positive pDq aged between 25 and 57 years (mean ± standard deviation: 44 ± 11 years). Thus, we cannot conclude that with rising age in the course of age a positive pDq result is more presumable.

There are some other limitations of the study based on a sheer questionnaire and

Discussion

In accordance to other studies our results provide evidence for an increased pain status in PwH when compared to controls (3, 23–24). Inflammatory conditions seem to play a major role for pain complaints in PwH. Regarding to molecular pathologic changes caused by haemophilic arthropathy, Acharya named some proinflammatory cytokines, which are involved in the development of haemophilic synovitis (25).

In general, proinflammatory cytokines are typical triggers in osteoarthritis or rheumatoid arthritis pain, as described in different studies. Schable et al. showed that especially the tumor necrosis factor-α, interleukin-1β and IL-6 play an important part in rheumatoid arthritis and osteoarthritis related pain, causing an increase sensitivity of the joint nociceptors (17, 26). These exact cytokines are involved in the destructive process during the development of haemophilic arthropathy (11). However, further studies have to analyse in greater detail the role of molecular causes of pain conditions in PwH.

As we hypothesised, our findings verified that non-neuropathic pain in PwH is prominent. On the basis of pDq results, non-neuropathic pain is verified in 79% of our patients. A peripheral increased excitability of C-fibres evoked by bleeding events, may lead to a secondary sensitisation and/or an increased activity of central nociceptive neurons in PwH.
cross-section elicitation. We are not able to verify if a more impaired joint is associated with a higher pDq-result. Also we cannot conclude a relation between the numbers of joint bleeding events and the pDq result. Further studies should clarify if these factors may influence the pDq result.

As a consequence of these data, it is necessary to investigate the pathogenesis of haemophilia related pain. As recently as the mechanisms of pain development and pain processing will be understood, evidence-based guidelines must be generated to cope the heterogeneity of pain in PwH adequately.

**Conclusion**

Although inflammatory pain is a central theme in PwH, neuropathic pain is present in approximately seven percent of the patients based on our study and may be a reason of an unsuccessful classical pain treatment in these patients. The pDq is a sensitive and specific tool to differ between the underlying pain mechanisms and should be included into a comprehensive pain diagnostic and treatment.

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**Conflict of interest**

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

**References**