Gaining insight into the complexity of pain in patients with haemophilia : state-of-the-art review on pain processing

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Abstract

Despite the high prevalence of recurrent, constant and/or widespread pain in patients with haemophilia (PwH), there is an immense lack of studies examining the (patho)physiology of pain in this population. This contrasts to the bulk of literature in other pain conditions, such as osteoarthritis, low back pain or rheumatoid arthritis. Understanding the complexity of pain allows to better asses and manage pain. In PwH the first priority is always to exclude bleeding as a cause of pain. An important next step in pain assessment is the evaluation of the predominant pain mechanism (i.e. nociceptive, neuropathic pain or altered central pain processing) as the treatment approach will be very different according to the underlying pain mechanism. Pain assessment should include both physiological and psychological components. This review summarizes the evidence regarding nociceptive, neuropathic and altered central pain processing in PwH and serves as a research agenda to prioritize pain research in PwH.

Key words: Pain, neuroplasticity, central nervous system, hyperexcitability, haemartrosis, haemophilia, exercise

Running head : Pain processing in patients with haemophilia

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1. Introduction

Pain is an important problem in patients with haemophilia (PwH). Surveys indicate that 85% of adult PwH suffered from pain during the last 6 months [1] and up to 89% of the patients reported that pain had interfered with their daily life the last 4 weeks [2]. Moreover, in patients with severe haemophilia less than 15% experience pain in only one or two regions, while more than 35% report pain in at least 5 regions [3].

Despite the magnitude of the problem, little is known about causal and/or maintaining factors of (chronic) pain in PwH. Traditionally, a differentiation is made between pain resulting from an acute bleed (haemarthrosis) and chronic pain originating from joint damage (arthropathy) [4]. This unconditional association (acute pain relates to bleeding and chronic pain is due to joint arthropathy) used in scientific literature and in clinical settings is remarkable. Firstly, the terms 'acute' and 'chronic' originally referred to a time frame and not to a specific underlying cause of pain [5, 6]. Secondly, both PwH and health care providers seem to be unable to differentiate the symptoms of haemarthrosis from those of arthropathy, seen the large overlap in clinical symptoms between both conditions [1, 4, 7, 8]. A study comparing perceptions regarding the aetiology of pain in PwH with ultrasound evaluation confirmed that a diagnosis based on the sole perception of pain is unreliable in the majority of the cases: the aetiology of pain (bleeding versus joint inflammation or other regional pain syndrome) was correctly judged in only 30% of the cases, either by the physician or the patient [8]!

The necessity to detect and treat acute bleeding in PwH is beyond dispute. But in contrast to other musculoskeletal pain conditions such as low back pain, osteoarthritis or rheumatoid arthritis, pain assessment in PwH is not well developed [9]. It is often limited to the evaluation of pain intensity and/or the use of non-validated pain questionnaires [9] with as main focus to detect a bleeding. Unsurprisingly, a survey among 22 haemophilia treatment centres in Europe revealed a lack of standardized pain assessment and a high variability in pain management [10]. Moreover, results from a national pain study in the United States indicate that 39% of patients report pain that is not well treated [11]. Several researchers therefore highlighted the urgent need to improve both pain assessment and pain management in PwH [9, 10, 12]. This can only been done if the (patho)physiology of pain in PwH is better understood.

2. Towards a better understanding of pain

The international association for the study of pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [5]. This definition implies that tissue damage might be present, but that it is not always necessary to have tissue damage to experience pain. For example in patients with low back pain or osteoarthritis, only weak associations exist between pain symptoms and tissue damage evaluated with medical imaging [13, 14]. Furthermore, spinal degeneration is present in the majority of healthy pain-free adults [15]. Also in PwH the relationship between pain intensity (VAS) and joint damage has been examined [16]. While strong correlations between VAS and radiological/clinical joint assessment (evaluated by the WFH joint clinical examination score and Petterson scale respectively) were observed for both knees (Spearman correlation scores above 0.50), it was not the case for the elbows and right ankle [16]. This confirms that a discordance can exist between pain experienced by the patient and the purported peripheral cause of pain, such as inflammation or joint damage [17]. During the last two decades, several research groups therefore examined mechanisms underlying pain more in detail. For example in patients with rheumatoid arthritis, inflammation certainly contributes to the pain, but it is not the only factor [17]. Chronic pain in several musculoskeletal conditions is believed to result from abnormal central pain processing, rather than from tissue damage [17-21]. Pain experience is a complex phenomenon and many other processes than bleeding or tissue damage play an important role as well. This can be better understood if the neurophysiology of pain is known.

When the body is confronted with a noxious stimulus (i.e. a stimulus that damages or threatens damage to normal tissue) ascending pathways relay this information from the periphery to the brain. Mechanical, chemical or thermal noxious stimuli will activate peripheral nociceptors. Nociceptive fibers (A-delta and C) will conduct the nociceptive signal to the dorsal horn of the spinal cord, the first central relay station for the processing of nociceptive stimuli [6, 19]. In the dorsal horn, a synaptic contact will be made with secondary or projection neurons, which will further transmit information from the dorsal horn to the thalamus, via the contralateral spinothalamic tract, and to the primary somatosensory cortex. The thalamus thus serves as second synaptic relay, where secondary neurons make synaptic contact with tertiary neurons [19]. Besides, direct connections are made from the dorsal horn to the medulla, brainstem and hypothalamus via the spinoreticular, spinomesenphalic and spinohypothalamic tract [19, 22]. Cortical and subcortical brain regions,

e.g. the anterior cingulate cortex, insula, prefrontal cortices, somatosensory cortices and amygdala, often referred to as the pain matrix, are activated during nociceptive processes and contribute to different aspects of pain perception, including the sensory quality of pain (i.e. the location, duration and intensity of pain), unpleasantness of pain, pain-related fear, pain memory and pain modulation [19, 22-24]. It is important to remember that pain is only experienced when information reaches the brain. Therefore the term nociception is used to refer to the nerve impulses following noxious stimulation, while pain perception is a complex sensory, affective, and sociocultural phenomenon requiring activity of the central nervous system and the brain [19, 25].

Pain is a dynamical phenomenon and nociceptive signals will be modulated at different levels of the central nervous system [19]. This modulation of impulses in the peripheral and central nervous system may increase or decrease the pain sensation [25]. Especially the descending pathways that carry signals from the brain to the dorsal horn are of major importance in pain modulation. Supraspinal structures, such as the ventrolateral medulla, periaqueductal gray and brainstem, have an crucial role in both inhibiting and facilitating nociceptive transmission and pain perception [22-24]. The body indeed disposes of a powerful endogenous pain control system. Endogenous inhibitory pathways are for example activated during exercise: a decrease in pain perception following exercise is observed in healthy (pain-free) subjects. This hypoalgesic effect of exercise, often called ‘exercise-induced analgesia’, is explained by the release of endogenous opioids, growth factors and other strong inhibitory mechanisms (‘descending inhibition’) orchestrated by the central nervous system and the brain [26]. The activity in descending pathways is not constant but is influenced by several factors such as level of vigilance, attention, expectation and/or stress [27], which may have a facilitating instead of inhibitory effect on nociceptive transmission.

Recent advances in pain neurophysiology have allowed to gain more insight into the role of the central nervous system and the brain in the processing of nociceptive information and in dysfunctions observed in patients with musculoskeletal pain [20, 28, 29]. Prolonged or strong activity may increase neuronal responsivity and cause sensitization [18]. Sensitization, defined as an increased response to stimulation, can appear in peripheral tissues and/or in the central nervous system including the brain. When pain persists, adaptation of unimodal nociceptors occurs, leading to an enhanced responsiveness of polymodal nociceptive endings by substances released from various sources [30]. This process is known as primary hyperalgesia or peripheral sensitization of

primary afferent nociceptors, and serves as a protective action to avoid further damage of injured tissues [20]. Secondary hyperalgesia refers to increased responsiveness of dorsal horn neurons [20]. While peripheral sensitization point towards a local phenomenon, central sensitization refers to increased responsiveness of central neurons and is therefore considered as a central (widespread) mechanism [18, 20]. Sensitization does however not mean that the condition is chronic, in acute pain the nervous system may sensitize as well. For example hypersensitivity to a variety of sensory stimuli, suggesting a sensitized central nervous system, has been demonstrated in patients soon after a whiplash injury [31].

In addition to an overactive ascending pathway, dysfunctions of the descending inhibitory pathways have been observed in many patients [32]. As mentioned above, an increase in pain thresholds (i.e. a decrease in pain perception) following exercise is observed in healthy (pain-free) subjects [26]. However, it became apparent during the last decade that a decrease in pain thresholds (i.e. an increase in pain perception) following exercise was observed in some chronic pain conditions such as fibromyalgia, chronic fatigue syndrome with widespread pain or chronic whiplash associated disorders [33-35]. This dysfunctional response to exercise indicates impaired endogenous inhibition [36]. Finally, activity in the descending pathway may facilitate nociceptive transmission as well. Products of the forebrain such as cognitions, attention and emotions, are able to modulate clinical pain experience and may contribute to the mechanism of central sensitization [37]. Seen their facilitating effect on nociceptive transmission, this is often called 'cognitive emotional sensitization' [38].

An important step in pain assessment is the evaluation of the predominant pain mechanism as the treatment approach will be very different according to the underlying pain mechanism [39]. A classification that is more and more used in patients with musculoskeletal pain is the differentiation between nociceptive pain, neuropathic pain and altered central pain processing [39, 40]. Nociceptive pain refers to pain originating from actual or threatened damage to non-neural tissue with activation of nociceptors. Neuropathic pain is defined as pain caused by a lesion or disease affecting the somatosensory nervous system [5]. The term nociceptive pain is used to describe pain occurring with a normally functioning somatosensory nervous system to contrast with the abnormal function observed in neuropathic pain [41]. The third category consists of patients with altered central pain processing (nociplastic pain). The international association for the study of pain defines the latter as pain arising from altered nociception despite no clear evidence of tissue damage causing the activation of

peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain [5]. To add to the complexity, mixed pain patterns are observed in patients [41]. For example a patient with low back pain that irradiates to the leg may suffer from a combination of nociceptive back pain (originating from a musculoskeletal structure such as disc, muscle, ligament or joint) and neuropathic pain in the leg, caused by irritation of the spinal nerve (radiculopathy). Also a combination of altered central pain with either nociceptive or neuropathic pain has been reported in patients with low back pain [42].

Most often, PwH are considered to suffer from nociceptive pain, but some researchers observed that a small proportion of the PwH have dominant neuropathic pain [43, 44]. Several questionnaires (e.g. painDETECT questionnaire, Leeds Assessment of Neuropathic Symptoms and Signs, DN4: Douleur Neuropathique en 4 Questions) exist that can be helpful in the diagnosis of neuropathic pain, in addition to the clinical examination and diagnostic tests (see [41] for a review). The question arises whether a proportion of PwH suffer from altered central pain mechanisms. This has not been studied before and will be detailed in the next paragraph.

3. Evidence for altered central pain processing in PwH?

3.1. Evidence for hypersensitivity to painful stimuli?

The examination of hyperalgesia (i.e. an increased pain response to a stimulus that normally provokes pain) is a frequently used method to identify hypersensitivity to painful stimuli, even in patients suffering from osteoarthritis or rheumatoid arthritis with severely damaged joints [17, 21, 45]. Primary hyperalgesia is reflected by decreased local pain thresholds, i.e. in the region of tissue damage or inflammation (peripheral sensitization). Secondary hyperalgesia refers to sensitization occurring within the central nervous system (central sensitization) and is manifested by decreased pain thresholds at remote places. Hence the widespread hyperalgesia typically observed in many chronic pain patients, e.g. those with rheumatoid arthritis [17, 45].

Mechanical pressure pain thresholds, defined as the point at which the pressure sensation turned to pain, were used in 4 studies to compare pain perception between PwH and healthy subjects in rest [44, 46-48]. While all studies revealed decreased pressure pain thresholds in at least one region (i.e. knees, ankles or elbows) in PwH compared to healthy subjects, one study observed a decrease in both knees and elbows [48] and in one study pressure pain thresholds in rest were significantly decreased at all locations, except the forehead [44]. A decrease in pressure pain thresholds at several locations, including locations absolutely unrelated to the

primary source of nociception (for example the sternum) in PwH clearly point towards widespread hyperalgesia, characteristic of central sensitization. This contrasts to the more localized hyperalgesia observed in Teyssler et al. (2014) and Krüger et al. (2017) which can be considered as peripheral sensitization.

Several factors might explain the differences in hypersensitivity (peripheral versus central sensitization) between these studies. Firstly, it is known that pressure pain thresholds might be influenced by several factors such as age [49] or gender [50]. The age range in the four studies varied between 12 and 69y, which might explain differences between studies or between individuals within one study. Secondly, two studies explicitly asked PwH to refrain from pain medication on the testing day, while no information about pain medication was given in the other studies. Taking pain medication before the evaluation of the pressure pain thresholds might influence the results. Future studies should therefore take this point into account (e.g. by testing pressure pain thresholds both before and after the intake of pain medication). Thirdly, some patients with a very recent history of bleeding were included, while others had no bleeding for more than 6 months. Finally, it is perfectly plausible that only part of the PwH suffer from altered central pain mechanisms. This is the case in patients with low back pain and osteoarthritis, in which only a subgroup of patients (i.e 15-30%) demonstrate signs of altered central pain mechanisms [20, 21]. If only a subgroup of PwH suffers from altered central pain mechanisms, using the mean data from the whole group will not be representative for all patients. Some researchers in the field of haemophilia already suggested to differentiate PwH based on pain mechanisms [43]. Future cross-sectional studies with a larger sample size are necessary to examine the proportion of patients with widespread hyperalgesia and other features of altered central pain processing. Even more important are longitudinal studies to examine the prognostic value of hypersensitivity to painful stimuli in PwH.

3.2. Evidence for a dysfunctional endogenous pain inhibition

Pain assessment often includes an evaluation of the endogenous pain inhibitory mechanisms. This can be examined by conditioned pain modulation paradigms [32], but also by studying the pain response in relation to exercise [36]. A dysfunctional response to exercise can be tested by experimentally inducing pain (e.g. evaluation of pressure pain thresholds) before and after an exercise protocol. The exercise protocol may consist of an aerobic endurance test, e.g. treadmill/cycling test, or may contain more local muscular contractions (e.g. static or dynamic resistance exercises) [33]. Of particular interest is the decrease in pressure

pain thresholds following exercise observed in some chronic pain populations, suggesting dysfunctional endogenous pain inhibition [33-35].

Only one study examined pain response in relation to exercise in PwH [44]. Twenty patients with moderate and severe haemophilia A and B underwent an evaluation of pressure pain thresholds at several locations before and after an aerobic exercise test on a treadmill. While pressure pain thresholds at all locations except the forehead were significantly lower compared to the values obtained in the healthy control subjects at baseline (see above), no significant decrease in pressure pain thresholds was observed in PwH following exercise [44]. Further research is necessary to confirm these results but the current evidence might suggest normal pain processing in response to exercise in PwH. This means that they will not have an increased pain sensation following exercise (as is the case in patients with fibromyalgia or chronic fatigue syndrome). The beneficial effects of physical activity in chronic musculoskeletal pain conditions are well-known [51] and exercise seem to be well tolerated by PwH. This should encourage health care providers to strongly motivate their PwH to exercise*. "So stop only advising exercise, prescribe it no*w" [52]!

3.3. Evidence for altered brain function in PwH?

Several brain areas (i.e. the pain neuromatrix) are activated during pain experiences. The overwhelming progression made in brain imaging techniques allow to unravel brain processing of pain based on a functional and structural non-invasive approach. Evidence revealing alterations in both brain structure and brain function in patients with chronic pain is growing [20, 29, 53], offering exciting perspectives in the study of pain. While the majority of the studies have a cross-sectional design, allowing to establish differences in brain morphology and/or brain function but without any conclusion regarding causal relationships, preliminary reports from longitudinal studies are now available. For example in patients with low back pain, longitudinal brain imaging studies accurately predicted the transition to chronic pain [54, 55]. Furthermore, effective treatment of chronic low back pain seems to reverse functional and structural brain abnormalities, suggesting that treating chronic pain can restore normal brain function in humans[56]. Finally, treatments in which the brain is directly targeted such as repetitive transcranial stimulation can have a potential utility in the management of chronic pain [57]. However, no studies examined brain structure or function in relation to experimentally induced pain in PwH until now. The research agenda in PwH should therefore include brain imaging studies as the results will add to a better understanding of pain.

4. Discussion

Understanding the complexity of pain allows to better asses and manage pain. However, studies regarding pain assessment in PwH are lacking, contrasting to the bulk of literature regarding pain assessment in other musculoskeletal pathologies. Unsurprisingly, a significant proportion of PwH report that their pain is not well managed. Undertreatment might have serious consequences, such limitations in activities of daily living, increased suffering and decreased quality of life [6].

The following part should be considered as a reflection to help clinicians in their pain assessment pending future studies. In PwH the first priority is always to exclude bleeding as a cause of pain. It might further be useful to employ the term “flare-up” to designate pain symptoms related to haemophilic arthropathy [4], in order to avoid strengthening misbeliefs of patients (i.e. the misbelief that acute pain always refer to a bleed). The second step consists of assessing the predominant pain mechanism. The majority of PwH suffer from nociceptive pain (pain originating for example from inflammation or from joint degeneration), but a small proportion of PwH demonstrate signs of neuropathic pain [43]. Probably also a subgroup of PwH suffer from altered central pain mechanisms, seen the widespread pain (pain at more than 5 locations), the decrease in pressure pain thresholds at several locations including regions not related to the primary source of nociception [46]. Future research should quantify the proportion of patients suffering dominant neuropathic pain or altered central pain processing. It is important to take the assessment of these pain mechanisms into account, as the treatment approach will vary considerably. The pharmacological treatment of neuropathic pain or altered central pain mechanisms is different from that of nociceptive pain and may include for example tricyclic anti-depressants and serotonin-norepinephrine reuptake inhibitors [17, 28, 58]. Future studies should also evaluate the effect of pain medication on pain assessment, as has been done in patients with chronic pain.

Thirdly, pain assessment in PwH should cover physiological and psychological components. Many guidelines advise to manage patients with pain from a biopsychosocial perspective, in which it is recognized that social, psychological as well as biomedical factors have a significant influence on pain and disability [59, 60]. It is out of the scope of the present review to describe the psychologic components of pain in detail. Health care providers should nevertheless remember that several psychological factors strongly contribute to the development of persistent pain and disability (see [61] for further reading). It is perfectly normal to have beliefs and emotions

about pain: limbic structures, such as the anterior cingulate cortex and the insula are involved in the affective and emotional component of pain [19] and the dorsolateral prefrontal cortex is responsible for the attention to pain. One study revealed that 85% of PwH reported that pain impacted their mood[3]. As beliefs and emotions about pain and illness, often called illness perceptions, will determine a patient's coping strategy [62], it is essential to include illness perceptions as well in the assessment of pain. In many chronic pain patients, negative illness perceptions are associated with maladaptive illness behaviour, dysfunction, poor treatment adherence and treatment outcome [63]. However, health care providers do not sufficiently address illness perceptions in patients with musculoskeletal pain [64].

Only a few studies assessed beliefs about haemophilia in PwH [65, 66]. These studies examined the beliefs about the illness (haemophilia) in general, not specifically the beliefs about pain. Preliminary results confirmed the relationship between illness perceptions and behavioral aspects (e.g. non-adherence to treatment) in PwH [65, 66]. However, the cross-sectional design of the studies does not allow to draw a conclusion regarding the causality of this relation. Future longitudinal studies are necessary to further explore the role of illness perceptions regarding pain in PwH.

5. Conclusion

Pain is a major problem in PwH. Preliminary evidence suggest that a proportion of PwH demonstrate signs of neuropathic pain and/or altered central pain mechanisms. Future studies are necessary to further develop pain assessment in PwH based on the knowledge in other chronic pain conditions, in order to tailor pain management for every patient.

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