Prevalence and burden of pain in Huntington's disease

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CHAPTER 6

Conclusions, discussion and future perspectives

The well-known signs and symptoms in Huntington's disease (HD) are the involuntary movements (chorea), the neurocognitive impairments and neuropsychiatric symptoms. Other symptoms, which are relatively less well-known, are, for example, weight loss, sleep disturbances, metabolic dysfunction, endocrine disturbances.[1,2] In addition, systemic symptoms such as cardiovascular, respiratory, gastrointestinal and urinary disorders are also prevalent in HD.[1,3] Pain may also be an important symptom; there is not, however, sufficient evidence to allow definitive conclusions to be drawn about whether pain is a prevalent and burdensome symptom in HD. The available studies are conflicting: some studies have demonstrated pain to be a prevalent and burdensome symptom [4–8], while others have suggested the opposite.[9–11] The overall aim of this thesis is to study in depth the prevalence and burden of pain across the entire spectrum of HD, as well as the prevalence of painful conditions and the use of analgesics in HD.

Conclusions

This thesis provides robust evidence that pain is a prevalent, burdensome and an apparently important symptom in HD (**chapters 2, 3** and **4**). The prevalence of pain, its detrimental impact on daily activities (pain interference), and subsequently the pain burden, vary, however, across the disease stages and 'age at symptom onset' (AO) groups of HD (**chapters 3** and **4**). For instance, pain is more prevalent in the late stage of HD and in late-onset HD (**chapters 3** and **4**). In addition, pain interferes with daily activities, in particular in the advanced stages of HD (**chapters 3** and **4**). The pain burden was significantly higher in the manifest stages of HD compared with healthy controls in the Registry- and HD-Enroll studies, and even compared to normative data of the general population and patients with chronic pain (**chapter 4**). Despite the severe pain burden, there seems to be undertreatment particularly in the advanced stages of HD (**chapter 4**). The development of symptoms as HD progresses, along with the distinct symptoms across the AO-HD groups, may influence the causes and the burden of pain, and subsequently the prescribed analgesics (**chapters 3** and **4**). For instance, the most frequently reported painful conditions in juvenile-onset HD (JHD) belonged to a cluster of painful conditions such as acquired deformities, restless-leg syndrome and post-traumatic pain, as opposed to back pain in adult-onset (AHD), and headache in late-onset HD (LoHD) (**chapter 4**). In all the AO-HD groups, paracetamol and NSAIDs were the analgesics most frequently used, followed by analgesics from the group of anti-epileptics, in particular in adolescent-onset juvenile HD (aJHD), and opioids in LoHD (**chapter 4**).

Pain management regimens rely on fundamental knowledge about the effect of HD on pain processing and also on studies enhancing pain assessment in HD. A comprehensive study design, including three different experimental pain protocols, was subsequently developed to assess the effect of HD on pain processing and to determine psychometric properties of an observational pain scale: the Pain Assessment in Impaired Cognition scale (PAIC15) (**chapter 5**). The feasibility of the experimental design had first to be tested (**chapter 5**).

Discussion

Prevalence and burden of pain in Huntington's disease

Pain is a prevalent and burdensome symptom in HD, varying across the disease stages and AO-HD groups, but is more prevalent and burdensome in the advanced stages of HD (**chapters 2, 3** and **4**). In contrast to these findings, preliminary studies demonstrated a subset of patients with HD who also had a coexisting painful condition; one would expect them to report pain; however, they expressed it less or not at all.[9,10] The underlying mechanisms responsible for this potential specific pain phenotype in HD remains unclear, due to the lack of studies addressing this specific phenomenon. In frontotemporal dementia(FTD), another neurodegenerative disease which has a similar neurocognitive and neuropsychiatric profile to HD, caregivers have reported a diminished pain response compared to other dementias.[12] In another study, however, caregiver reports revealed a diverse phenomenology, both a decreased and increased responsiveness to pain in FTD.[13] An experimental study proposed that the potential loss of response to pain in FTD, may be the result of disturbances in the processing of the affective-motivational components (*e.g.* suffering) of pain.[14] Furthermore, in (severe) neurocognitive disorders, pain may not be recognized, as it manifests itself through challenging behaviors, such as irritability, socially disruptive behavior, wandering, depression and apathy.[15] These behaviors can be misinterpreted as neuropsychiatric symptoms in neurocognitive disorders, leading to treatment with psychotropic rather than analgesic medication.[16] Due to the lack of studies, the effect of HD on the various components of pain, as well as the potential association in HD between pain and challenging behaviors, are not yet well understood.

The estimated mean prevalence of pain (**chapter 2:** 41%) in HD is similar to that demonstrated in Parkinson's disease (PD).[17] In PD, the combination of the symptoms, as well as the hypersensitivity to pain (hyperalgesia), is proposed to be related to dysfunction of the basal ganglia-thalamocortical circuits (dopamine deficiencies); this is thought to contribute to the high prevalence and burden of pain in PD.[18,19] A similar underlying neurological mechanism may be present in HD. The striatum (also part of the basal ganglia) is a neurological area particularly susceptible to HD. It plays an important role in pain processing (pain modulation and endogenous analgesia), via the descending pathway.[20–22]

In PD, irrespective of the disease stages, pain is one of the bothersome non-motor symptoms, contributing to PD-related disability and impaired Quality of Life (QoL).[17,23–25] Studies assessing the pain burden compared to other common burdensome symptoms of HD, as well as the associated factors and the effect of pain on the QoL in HD, are limited.[26] In PD, the prevalence of painful conditions is assessed by an internationally agreed comprehensive classification system.[17,19] It can be stated that in both PD and HD, musculoskeletal (nociceptive) pain, such as limb and back pain, is more prevalent than neuropathic pain (**chapters 3** and **4**).[17,19,23] The risk of undertreating pain, which has been repeatedly addressed in PD [17,19,23], also seems to be present in HD (**chapter 4**). More studies are, however, necessary to confirm this in HD.

In summary, although the phenotype and neuropathology of PD differ from HD, there are similarities. Pain as a symptom in HD should, therefore, be regarded as being just as important as it is in PD and its significance recognized.

Pain assessment in Huntington's disease

Adequate pain assessment, including valid and reliable pain scales, is essential to prevent undertreatment of pain in HD. To our knowledge, studies testing the psychometric properties of pain scales in HD are too limited to incorporate in guidelines for HD pain management. International agreements for pain assessments in neurodegenerative diseases recommend using unidimensional (numerical rating scale [NRS], verbal descriptor scale [VDS], facial pain scale [FPS] and colored analogue scale [CAS]), multidimensional self-reported pain scales (Brief Pain Inventory [BPI] and McGill Pain Questionnaire [MPQ]) and, if necessary, an observational pain scale.[27,28] The FPS consists of seven faces: from a neutral face (no pain) to a grimacing face (worst pain); this may be less appropriate for use in HD, due to the compromised function for recognizing facial expression of pain in HD.[29,30] In addition, the use of self-reported pain scales, which is the gold standard, might be challenging, due to the progressive neurocognitive impairments, language and speech disabilities, particularly present in patients in the late stage of HD. To bypass this issue, the use of an observational pain scale is, therefore, recommended.[27,28] A recent study involving various neurocognitive disorders (mild cognitive impairment, HD, dementia) demonstrated promising results concerning the inter-rater reliability (interclass coefficient of > 0.75) of an observational pain scale named 'the Pain Assessment in Individuals with Cognitive Impairment'(PAIC15).[31] In that particular study, however, there were several methodological issues which introduced bias. These included a heterogenous group of patients and the lack of individually tailored stimuli intensity. The latter increases the risk of variability in the pain intensity experienced. The developed experimental design, focused solely on HD (**chapter 5**), employs individually tailored stimulus intensities, thereby reducing the risk of such variability.

Methodological considerations

Registry and Enroll- HD studies

The international datasets of the Registry- and Enroll- HD study which were used, include large sample sizes of genetically confirmed HD gene mutation carriers (with and without signs) as well as controls. The databases are of high quality and have been monitored for quality and accuracy using a risk-based monitoring approach. The use of these databases provided a unique opportunity to assess pain using different pain assessment scales, and, as a result, to extend the knowledge about pain in HD. Furthermore, it enabled our findings to be stratified across various disease stages and AO-HD groups, so that pain could be assessed throughout the HD spectrum. Although, the findings are based on large sample sizes and are, therefore, robust, the risk of selection bias must be considered, thus challenging the generalizability of the findings to the HD population. In both Registry- and Enroll-HD studies, the data are primarily collected from Europe and Northern America. One should be cautious when generalizing the findings world-wide, considering the complex interaction of personal, social, economic and cultural factors in the prevalence and the experience of pain.[32] In addition, patients particularly defined as late stage in the Registry- and Enroll-HD study are not representative of patients admitted to specialized HD-nursing homes. Patients included in the Registry- and Enroll-HD studies were physically and mentally able, or, with varying degrees of assistance from support systems, able to visit the clinical site for the study assessments as opposed to patients admitted to specialized HD-nursing homes. The sample size of the Juvenile-HD groups in the studies of this thesis were, in contrast to adult onset-HD groups, relatively small. Furthermore, in the Registry- and Enroll-HD study, the pain assessments were not part of the core assessment; there was no background information about why a pain assessment was or was not carried out. As a result, data were missing, however, multiple imputations did not reveal an impact of the missing data on the outcomes.

Self-reported pain scales

The self-reported pain scales included in both studies, bodily pain items of the Short-Form Health Survey-12 and 36 (SF12 and SF36, respectively), are too limited to assess pain extensively enough. In accordance with international agreements, it is advised that, besides uni-dimensional self-reported pain scales, multi-dimensional self-reported pain scales, such as the BPI and MPQ, are used to assess the different domains of pain.[27,28] Such multi-dimensional self-reported pain scales are, however, not included in HD registries. Furthermore, despite the fact that self-reported pain scales are considered as the gold standard in pain assessment, neurocognitive disturbances, which are prevalent in HD, may also interfere with pain assessment in the Registry- and Enroll-HD study.[33] As these assessments are performed only once a year in both studies, a risk of recall bias is certainly present.

Experimental pain protocol: a feasibility study

The comprehensive experimental pain protocol (**chapter 5**) includes well defined groups of patients with HD which will be exposed to individually tailored stimulus intensities. Tailoring the painful stimuli individually diminishes the risk of differences in the experienced pain intensity and subsequently biasing the findings. Due to methodological and ethical consideration, only patients in the early and middle stage will be included in this pilot study to assess the feasibility of the experimental pain protocol, and not those in the late stage of HD, even though the use of an observational pain scale is indicated to be used particularly in the latter group. Consequently, a compromised ecological validity may be present, biasing the generalizability of the findings to the patients in HD-specialized nursing homes.

Future perspectives

Clinical practice

To enhance the awareness of pain as an important symptom in HD, several recommendations are proposed for clinical practice.

Firstly, it is recommended to conduct pain assessments in patients with HD, based on clinical judgement or on demand. Furthermore, to decrease the risk of under-recognition and undertreatment (*i.e.* pharmacological and non-pharmacological) of pain in HD, it is recommended that pain assessment is incorporated as a core assessment in the Dutch national care agreements (Dutch translation: Zorgprogramma extra- en intramurale zorg voor patiënten met de ziekte van Huntington).[34,35] In accordance with the Dutch care agreements, patients with HD are annually followed by standardized assessments; however, pain assessments do not yet form part of the core assessments.[34,35] Furthermore, to enhance awareness of pain more at international level, one might also consider adding a (short) pain assessment to the Unified Huntington Disease Rating Scale (UHDRS), which is an internationally valid, agreed and frequently used scale for assessing the various symptoms and to determine the severity of HD.[36] Finally, to our knowledge, pain is not yet addressed as an important symptom in (inter)national guidelines and specialized textbooks for HD. This omission from the literature should be resolved, to diminish the risk of underestimation, under-recognition and, subsequently, undertreatment of pain in HD.

Scientific field

For appropriate assessment of pain, the methodological quality and sufficiency of measurement properties, such as the reliability, validity, responsiveness, and interpretability of the various pain scales, should also be tested in HD to ascertain which pain scale is deemed appropriate to use in HD.[37] Until then, in accordance with international guidelines, unidimensional (NRS, VRS or CAS) and multidimensional self-reported pain scales (BPI and MPQ) are deemed to be the most appropriate for use and potentially to be adopted in ongoing longitudinal studies, such as the Enroll-HD 2.0 study.[27,28] Including a pain assessment as part of the core assessment in such large international ongoing longitudinal studies will be a fast and efficient way to obtain a better understanding about pain in HD.

Secondly, the experimental design, as described in **chapter 5**, be deemed feasible, the psychometric properties of various observational pain scales can be assessed in HD. The findings of these studies should, however, be translated to clinical practice. Since observational pain scales rely partly on the assessment of the facial expression, it is also recommended that the effect of HD (*i.e.* facial chorea) on the facial expression of pain be studied more extensively using the Facial Action Coding System (FACS).[38] The FACS enables one to determine which action units in the face, from a psychometric perspective, are deemed essential for recognizing pain and subsequently to be included in an observational pain scale.[38] A potentially interesting and fast developing area is the development of facial expression recognition software. Combining facial expression recognition software with observational pain scales, may facilitate and simplify the recognition of pain in clinical practice.

Thirdly, studies assessing the effect of HD on pain processing and other dimensions of pain, and studies to determine the causes of pain and to ascertain whether HD causes pain independently, will provide more fundamental knowledge. In addition to Quantitative Sensory Testing, neurophysiological techniques (electroencephalogram or laser evoked potentials [LEPs]) and imaging studies (functional Magnetic Resonance Imaging or Positron Emission Tomography [PET]) will help unravel the effect of HD on pain processing. Both PET and LEPs studies have shown promising distinct patterns in HD.[39–42] To our knowledge, there is a lack of other neurophysiological studies assessing the effect of HD on pain processing.

Fourthly, to improve pain management regimens in HD, it is recommended that a HD-specific taxonomy of the various causes of pain in HD are developed, in analogy with PD. A taxonomy of pain in HD may also help to determine whether HD-specific painful conditions exist.[19] Future studies addressing the causes of pain in HD should account for the complex reciprocal associations between all symptoms. Network modeling, such as (un)directed acyclic graphs, might be an appropriate method to reveal the association of the various symptoms in HD and pain.

Finally, qualitative studies, including semi-structured interviews in HD, are warranted to gain a better understanding of the personal experience of pain in terms of the quality, the impact and evolution of pain as HD progresses and the satisfaction with the pain management regimens received.

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