Prevalence and burden of pain in Huntington's disease

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APPENDICES

Summary

Huntington's disease (HD) is a rare autosomal-dominant neurodegenerative disease, caused by an increased number of Cytosine-Adenine-Guanine (CAG) repeats in the *huntingtin* gene. The resulting abnormally elongated polyglutamine repeat in the *huntingtin* protein causes neuronal loss in the brain. In particular, the striatum is susceptible to this abnormal huntingtin protein. Neurodegeneration of the striatum is already developing before the onset of motor symptoms. HD can be clinically divided into a premanifest and manifest stage, based, respectively, on the absence or presence of motor symptoms.

Based on the functional capacity the symptomatic stage is divided in early , middle and late stage. In the manifest stage, motor symptoms such as chorea, dystonia and balance disturbance are present, as opposed to the premanifest stage. Furthermore, HD is divided into 'juvenile–onset' (<21 years), 'adult-onset' (≥ 21 and ≤59ste years) and 'late-onset' (≥ 60ste years) on the basis of 'age at symptom onset' (AO). There is an inverse association between CAG repeat length and the 'age at symptom onset'. More specifically symptoms of HD tend to become manifest at an earlier age with a longer CAG repeat length.

As well as motor symptoms, HD is characterized by *neurocognitive impairments* (e.g. decreased information processing, attention, memory and executive disturbances), *neuropsychiatric symptoms* (e.g. irritability, depression, anxiety, apathy) and other *non-motor symptoms* (e.g. weight loss, sleep disturbances, metabolic and endocrine disturbances). Subtle neurocognitive and neuropsychiatric symptoms can be present 10 -15 years before the motor-onset of HD. As HD progresses, patients commonly develop a major neurocognitive disorder (dementia).

Although pain may not be recognized as such, it may well be an important symptom in HD. Studies which specifically address pain in HD are limited, and demonstrate conflicting findings: some studies have demonstrated pain to be a prevalent and burdensome symptom in HD, while others have suggested the opposite. The discrepancy in findings may be due to small and heterogeneous groups of patients with HD included in these studies. Hence, given the limited number of studies available, it is premature to draw definitive conclusions about whether pain is a prevalent and burdensome symptom in HD. Studies addressing pain in HD are, therefore, needed, particularly because pain affects the Quality of Life (QoL) and current treatments are primarily focused on relieving the symptoms of HD in order to improve the QoL (**chapter 1**).

In this thesis, pain was extensively and systematically studied to determine whether it is a prevalent and burdensome symptom in HD. A systematic review and meta-analysis were conducted (**chapter 2**); various world-wide datasets were used to assess pain as extensively as possible throughout the spectrum of HD (**chapters 3** and **4**). Subsequently, the prevalence of pain, its detrimental impact on daily activities (*i.e.* pain interference), painful conditions and the use of analgesics, as well as the pain burden, have been assessed across the different disease stages and AO-HD groups. In order to improve pain management regimens in HD, we developed a method of assessing the effect of HD on pain processing and determining the psychometric properties of an observational pain scale. The study design included different experimental pain protocols (**chapter 5**).

The systematic review and meta-analysis revealed that pain is a prevalent symptom in the HD population, with an estimated mean prevalence of 40% (**chapter 2**). The prevalence of pain ranged, however, from 10% to 75%. It was not possible to stratify the prevalence of pain across the disease stages or AO-HD groups. Therefore, to extend the knowledge about pain in HD, we studied the prevalence of pain interference, painful conditions and the use of analgesics across the disease stages of HD using the dataset of the Enroll-HD study (**chapter 3**). Although they differ across the diseases stages of HD, the overall prevalence of pain interference was 34%, of painful conditions 17% and of analgesic use 13%. For instance, pain interference was more prevalent in the middle stage of HD (42%), whereas the prevalence of painful conditions was lower in the middle and late stages of HD (15% and 12%, respectively) compared to healthy controls (**chapter 3**).

To further extend what is known about pain, the dataset of the Registry-HD study was used including more extensive pain assessment scales (**chapter 4**). The prevalence of pain, pain interference, and subsequently the pain burden vary across the disease stages and OA-HD groups. Pain was most prevalent in the late stage (47%); pain interference in the middle stage (43%) of HD. In the dataset of the Registry-HD study, both pain (53%) and pain interference (50%), were most prevalent in late-onset HD. Furthermore, the study revealed that pain is a burdensome symptom in HD, particularly in the manifest stages, when the pain burden was even significantly greater, compared to patients with chronic pain. It is thus striking that there seems to be a risk of undertreatment, in particular during the late stage of HD (**chapter 4**).

There is an overlap between the findings reported in **chapters 3** and **4** regarding the prevalence of pain and pain interference compared to the prevalence of painful conditions and analgesic use. In both chapters it was demonstrated that while pain and

pain interference were more prevalent in the manifest stages of HD, the prevalence of painful conditions and analgesic use did not increase accordingly. Firstly, one can speculate that the discrepancy may indicate that HD itself may cause pain, a symptom of which physicians may not be sufficiently aware of to allow proper diagnosis. Secondly, one can propose that development of the symptoms as HD progresses, along with the distinct symptoms across the AO-HD groups, may influence the causes of pain and the prescribed analgesics.

Pain management regimens rely on fundamental knowledge about the effect of HD on pain processing and also on studies improving the pain assessment in HD. To address both issues, we developed a comprehensive study design, including three different experimental pain protocols (**chapter 5**). On medical-ethical grounds and from a methodological perspective, it was deemed appropriate to initially assess the feasibility of the experimental design in patients in the early and middle stage of HD (**chapter 5**). With regard to pain processing, the experimental design allows the option of assessing disturbances in endogenous pain modulation responsible for facilitation and inhibition of pain. The striatum, which is a neurological area susceptible to HD, plays an important role in endogenous pain modulation. Disturbances in pain modulation might, therefore, be expected in HD. The experimental design also allows testing of psychometric properties (intra-rater, inter-rater and test-retest reliability) of an observational pain scale, the Pain Assessment in Impaired Cognition scale (PAIC15). An observational pain scale plays a crucial role in the recognition and assessment of pain, in particular in patients who have difficulty reporting pain due to progressive neurocognitive disturbances, language and speech disabilities.

The overall conclusions are presented in **chapter 6**, followed by a discussion and recommendations for clinical practice and the wider scientific field. In conclusion, this thesis provides robust evidence that pain is a prevalent, burdensome and, apparently, an important symptom in HD. Nevertheless, there does seem to be a risk of undertreatment with analgesics. It is strongly advised that healthcare professionals remain particularly vigilant for pain in HD and the risk of undertreatment with analgesics. Regarding the methodological constraints of the current thesis, as addressed in **chapter 6**, prospective studies, including various unidimensional, multidimensional pain assessment scales and other outcomes for measuring pain burden, are warranted, to foster the understanding of pain in HD. In addition, fundamental studies are needed to bridge the knowledge gap regarding the effect of HD on pain processing. Thirdly, given the typical motor symptoms of HD (*e.g.* chorea), pain recognition and assessment may pose a particular challenge compared to other neurodegenerative diseases. It is recommended that well-established pain

observational scales are studied to assess whether they are valid and reliable for use in the clinical field, and to determine whether a HD-tailored pain observation scale should be developed.