Prevalence and burden of pain in Huntington's disease

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CHAPTER 1

Introduction

1. Introduction

1.1 Huntington's disease

Huntington's disease (HD) is a rare, progressive, autosomal dominant, neurodegenerative disease. Its prevalence is estimated to be 5-10 per 100,000.[1] HD is caused by a cytosine-adenine-guanine (CAG) trinucleotide repeat expansion in the huntingtin gene, which encodes the huntingtin protein.[2] A CAG repeat length of 36 and higher is associated with nearly full manifestation of symptoms and signs.[3] The variability in the 'age at symptom onset' of HD (AO-HD) is approximately 50-70% attributable to the length of the CAG repeat and is inversely correlated with age.[3,4] The most important symptoms of HD can be attributed to central nervous system (CNS) degeneration. In the brain, HD leads to massive atrophy and neuronal cell death of the GABAergic medium spiny neurons in the striatum, which project to different neurological areas in the brain.[5,6] HD is classified as a multisystem neurodegenerative disorder, characterized by progressive neurodegeneration, affecting not only the striatum, but also the cerebral neo- and allocortex, thalamus, pallidum, brainstem and cerebellum.[6–8] As no curative treatment exists to prevent or delay onset or slow down progression, current treatment is focused on relief of symptoms to improve Quality of Life.

1.2 Huntington's disease and the clinical symptoms

HD is characterized by a mixture of signs and symptoms including involuntary movements (chorea), neurocognitive impairments and neuropsychiatric symptoms. Besides this well-known triad of symptoms, other non-motor symptoms are described in HD, such as weight loss, sleep disturbances, metabolic dysfunction, endocrine disturbances and systemic symptoms such as cardiovascular, respiratory, gastrointestinal and urinary disorders.[9–11] The 'age at symptom onset' varies between 2 and 85 years, with a mean disease duration of 17-20 years.[9] In addition, patients with symptom onset before the age of 21 years, irrespective of their current age, are referred to as juvenile-onset HD.[12–15] Disease onset is typically defined by the manifestation of the characteristic chorea.[9] Other motor symptoms, such as oculomotor signs, hypokinesia, can occur in HD.[9,16] HD can be divided into the premanifest or manifest stage, based respectively on the absence or presence of motor symptoms.[17]

Although the motor symptoms are the hallmark for determining disease onset, subtle neurocognitive and neuropsychiatric symptoms can be present 10-15 years before motor signs occur.[18,19] The neurocognitive profile in the premanifest stage includes disturbances in the psychomotor speed, emotion recognition and subtle executive dysfunction. In addition to these deficits, in the manifest stage, disturbances of

attention, memory and worsening of executive functioning are prevalent.[20] As HD progresses, patients often develop a major neurocognitive disorder.[9] In addition to the neurocognitive profile in HD, a variety of neuropsychiatric symptoms are seen in HD, depression, apathy, irritability, aggression, obsessive-compulsive disorder, anxiety, and psychosis being the most prevalent.[21,22] Apathy has been demonstrated as the key neuropsychiatric symptom in HD, both in the premanifest and the manifest stages, but particularly in the advanced stages(50%).[21] In contrast, psychosis is less prevalent (3-11%) in HD compared to the other neuropsychiatric symptoms.[21]

Given the neuropathological changes and the clinical symptoms and signs of HD, one might expect this could influence the subjective experience of pain. For instance, the striatum is part of the descending pain modulatory and endogenous analgesia system of the CNS, which can both suppress and facilitate pain.[23–26] Dysfunction in the descending pain modulatory system is associated with different chronic pain conditions, such as fibromyalgia, chronic tension headache, and complex regional pain syndrome, as well as with an increased risk of developing chronic pain following interventions.[27–30] Furthermore, prevalent neuropsychiatric symptoms of HD such as depression and anxiety are both important in the experience of pain, in terms of the experienced intensity, burden, risk for chronification of pain and functional disability.[31–35]

1.3 Huntington's disease and pain

Studies specifically addressing pain in HD are limited, mostly consisting of case reports and preliminary studies of small, heterogenous patient groups.[36–41] There are discrepancies in the findings: some studies have demonstrated pain as a prevalent and burdensome symptom [36–39,42], while others have suggested the opposite.[40,41,43] The available experimental studies have demonstrated slower pain processing at the spinal cord level in the premanifest and early stage of HD compared to healthy controls.[44–46] As speculated by these studies, the slower pain processing might indicate an underlying mechanism which potentially reduces the pain burden in patients with HD. Given the conflicting and limited number of studies available, it is premature to draw a definitive conclusion about whether pain is a prevalent and burdensome symptom in HD. More extensive studies addressing pain in HD are warranted. 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. The prevalence refers to the proportion of the HD population reporting pain at a given time, while the pain burden captures the severity and impact of pain on individuals' lives.[47–49]

First, a systematic review and meta-analysis were conducted to assess the prevalence and the burden of pain in HD (**chapter 2**). We reviewed and analyzed studies which assessed pain, among other symptoms, in HD. To further explore the prevalence of different pain outcomes across the different stages of HD, a cross-sectional study was conducted using the database from the Enroll-HD study, a large international observational study (**chapter 3**). In order to validate the findings of the Enroll-HD study and to assess pain with other pain assessment scales across different AO-HD groups, another large international database was used (Registry-HD study) (**chapter 4**). To improve pain management regimens in HD, a comprehensive study design, including three different experimental pain protocols was developed. Subsequenlty, providing the possibility 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 must first be tested (**chapter 5**). The conclusions, discussion and future perspectives are presented in **chapter 6.**

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