

Prevalence and burden of pain in Huntington's disease Sprenger, G.P.

Citation

Sprenger, G. P. (2025, September 4). *Prevalence and burden of pain in Huntington's disease*. Retrieved from https://hdl.handle.net/1887/4259702

Version: Publisher's Version

Licence agreement concerning inclusion of doctoral

License: thesis in the Institutional Repository of the University

of Leiden

Downloaded from: https://hdl.handle.net/1887/4259702

Note: To cite this publication please use the final published version (if applicable).





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-quanine (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

CHAPTER 1

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. Subsequently, 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**.

References

- Medina A, Mahjoub Y, Shaver L, Pringsheim T. Prevalence and Incidence of Huntington's Disease: An Updated Systematic Review and Meta-Analysis. Mov Disord. 2022;37(12):2327-2335. doi:10.1002/mds.29228
- 2. MacDonald ME, Ambrose CM, Duyao MP, et al. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell*. 1993;72(6):971-983. doi:10.1016/0092-8674(93)90585-E
- 3. Langbehn DR, Brinkman RR, Falush D, Paulsen JS, Hayden MR. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. *Clin Genet*. 2004;65(4):267-277. doi:10.1111/j.1399-0004.2004.00241.x
- Wexler NS, Lorimer J, Porter J. Venezuelan kindreds reveal that genetic and enviromental factors modulate Huntington's disease age of onset. *Proc Natl Acad Sci USA*. 2004;101(10):3498-3503. doi:10.1159/000076707
- 5. Vonsattel JPG. Huntington disease models and human neuropathology: similarities and differences. *Acta Neuropath*. 2010;115(1):55-69. doi:10.1007/s00401-007-0306-6.Huntington
- Halliday GM, McRitchie DA, Macdonald V, Double KL, Trent RJ, McCusker E. Regional specificity of brain atrophy in Huntington's disease. *Exp Neurol*. 1998;154(2):663-672. doi:10.1006/exnr.1998.6919
- 7. Ross CA, Tabrizi SJ. Huntington's disease: from molecular pathogenesis to clinical treatment. *Lancet Neurol*. 2011;10(1):83-98. doi:10.1016/S1474-4422(10)70245-3
- 8. Rüb U, Seidel K, Heinsen H, Vonsattel JP, den Dunnen WF, Korf HW. Huntington's disease (HD): the neuropathology of a multisystem neurodegenerative disorder of the human brain. *Brain Pathol.* 2016;26(6):726-740. doi:10.1111/bpa.12426
- 9. Roos RAC. Huntington's disease: a clinical review. Orphanet J Rare Dis. 2010;5(40):1-8.
- 10. Mehanna R, Jankovic J. Systemic Symptoms in Huntington's Disease: A Comprehensive Review. *Mov Disord Clin Pract*. 2024;(February):1-12. doi:10.1002/mdc3.14029
- Aziz NA, Swaab DF, Pijl H, Roos RAC. Hypothalamic Dysfunction and Neuroendocrine and Metabolic Alterations in Huntington'S Disease: Clinical Consequences and Therapeutic Implications. Rev Neurosci. 2007;18(3-4):223-252. doi:10.1515/REVNEURO.2007.18.3-4.223
- 12. Quarrell O, O'Donovan KL, Bandmann O, Strong M. The prevalence of juvenile Huntington's disease: a review of the literature and meta-analysis. *PLoS Curr.* 2012;4. doi:10.1371/4f-8606b742ef3
- 13. Quarrell OWJ, Nance MA, Nopoulos P, et al. Defining pediatric huntington disease: Time to abandon the term Juvenile Huntington Disease? *Mov Disord*. 2019;34(4):584-585. doi:10.1002/mds.27640
- 14. Bakels HS, Roos RAC, van Roon-Mom WMC, de Bot ST. Juvenile-Onset Huntington Disease Pathophysiology and Neurodevelopment: A Review. *Mov Disord*. 2022;37(1):16-24. doi:10.1002/mds.28823
- 15. Tabrizi SJ, Schobel S, Gantman EC, et al. A biological classification of Huntington's disease: the Integrated Staging System. *Lancet Neurol*. 2022;21(7):632-644. doi:10.1016/S1474-4422(22)00120-X

CHAPTER 1

- Hicks SL, P.A. Robert M, V.P. Golding C, Tabrizi SJ, Kennard C. Oculomotor Deficits Indicate the Progression of Huntington's Disease. Vol 171. Elsevier Masson SAS; 2008. doi:10.1016/ S0079-6123(08)00678-X
- Novak MJU, Tabrizi SJ. Huntington's Disease: Clinical presentation and treatment. *Int Rev Neurobiol*. 2011;98:297-323. doi:10.1016/B978-0-12-381328-2.00013-4
- 18. Paulsen JS, Langbehn DR, Stout JC, et al. Detection of Huntington's disease decades before diagnosis: The Predict-HD study. *J Neurol Neurosurg Psychiatry*. 2008;79(8):874-880. doi:10.1136/jnnp.2007.128728
- 19. Tabrizi SJ, Scahill RI, Owen G, et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: Analysis of 36-month observational data. *Lancet Neurol*. 2013;12(7):637-649. doi:10.1016/S1474-4422(13)70088-7
- 20. Dumas EM, Bogaard S van den, Middelkoop H, Roos RAC. A review of cognition in Huntington's disease Eve. *Front Bio.* 2013;5:1-18.
- 21. Duijn E Van, Craufurd D, Hubers AAM, et al. Neuropsychiatric symptoms in a European Huntington's disease cohort (REGISTRY). *J Neurol Neurosurg Psychiatry*. 2014;85:1411-1418. doi:10.1136/jnnp-2013-307343
- 22. Dale M, van Duijn E. Anxiety in Huntington's Disease. *J Neuropsychiatry Clin Neurosci.* 2015;27(4):262-271. doi:10.1176/appi.neuropsych.14100265
- 23. De Ridder D, Vanneste S, Smith M, Adhia D. Pain and the Triple Network Model. *Front Neurol*. 2022;13(March):1-13. doi:10.3389/fneur.2022.757241
- 24. De Ridder D, Vanneste S. *The Bayesian Brain in Imbalance: Medial, Lateral and Descending Pathways in Tinnitus and Pain: A Perspective*. Vol 262. 1st ed. Elsevier B.V.; 2021. doi:10.1016/bs.pbr.2020.07.012
- 25. Barceló AC, Filippini B, Pazo JH. The striatum and pain modulation. *Cell Mol Neurobiol*. 2012;32(1):1-12. doi:10.1007/s10571-011-9737-7
- Borsook D, Upadhyay J, Chudler EH, Becerra L. A key role of the basal ganglia in pain and analgesia - insights gained through human functional imaging. Mol Pain. 2010;6(27):1-17.
- Yarnitsky D, Crispel Y, Eisenberg E, et al. Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. *Pain*. 2008;138(1):22-28. doi:10.1016/j. pain.2007.10.033
- Seifert F, Kiefer G, Decol R, Schmelz M, Maihöfner C. Differential endogenous pain modulation in complex-regional pain syndrome. *Brain*. 2009;132(3):788-800. doi:10.1093/brain/ awn346
- 29. Lautenbacher S, Rollman GB. Possible Deficiencies of Pain Modulation in Fibromyalgia. *Clin J Pain*. 1997;13(3). https://journals.lww.com/clinicalpain/fulltext/1997/09000/possible__deficiencies_of_pain_modulation_in.3.aspx.
- Pielsticker A, Haag G, Zaudig M, Lautenbacher S. Impairment of pain inhibition in chronic tension-type headache. *Pain*. 2005;118(1). https://journals.lww.com/pain/fulltext/2005/11000/impairment of pain inhibition in chronic.28.aspx.

- 31. Meints SM, Edwards RR. Evaluating psychosocial contributions to chronic pain outcomes. *Prog Neuro-Psychopharmacology Biol Psychiatry*. 2018;87(December 2017):168-182. doi:10.1016/j.pnpbp.2018.01.017
- 32. Severeijns R, Vlaeyen JWS, Van Den Hout MA, Weber WEJ. Pain catastrophizing predicts pain intensity, disability, and psychological distress independent of the level of physical impairment. *Clin J Pain*. 2001;17(2):165-172. doi:10.1097/00002508-200106000-00009
- 33. Khan RS, Ahmed K, Blakeway E, et al. Catastrophizing: A predictive factor for postoperative pain. *Am J Surg*. 2011;201(1):122-131. doi:10.1016/j.amjsurg.2010.02.007
- 34. Gatzounis R, den Hollander M, Meulders A. Optimizing Long-term Outcomes of Exposure for Chronic Primary Pain from the Lens of Learning Theory. *J Pain*. 2021;22(11):1315-1327. doi:10.1016/j.jpain.2021.04.012
- 35. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and Pain Comoribidity. *Arch Intern Med.* 2003;163:2433-2445. doi:10.3109/9780203090640-14
- 36. Albin RL, Young AB. Somatosensory phenomena in Huntington's disease. *Mov Disord*. 1988;3(4):343-346. doi:10.1002/mds.870030411
- 37. Scherder E, Statema M. Huntington's disease. *Lancet (London, England)*. 2010;376(9751):1464. doi:10.1016/S0140-6736(10)61990-3
- 38. Kosinski CM, Schlangen C, Gellerich FN, et al. Myopathy as a first symptom of Huntington's disease in a Marathon runner. *Mov Disord*. 2007;22(11):1637-1640. doi:10.1002/mds.21550
- 39. Killoran A, Biglan K, Julian-Baros E, Yoritomo N, Ross C. Analysis of Analgesic Use in Pre-Manifest Huntington Disease. *Neurology*. 2013;80(7):P07.208. https://n.neurology.org/content/80/7_Supplement/P07.208.
- 40. Andrich JE, Wobben M, Klotz P, Goetze O, Saft C. Upper gastrointestinal findings in Huntington's disease: Patients suffer but do not complain. *J Neural Transm*. 2009;116(12):1607-1611. doi:10.1007/s00702-009-0310-1
- 41. Ferrer-Inaebnit E, Segura-Sampedro JJ, Molina-Romero FX, Xavier González-Argenté. Obstruction and ischaemia due to caecal volvulus in Huntington's chorea. *Gastroenterol Hepatol.* 2020;43(10):633-634.
- 42. Underwood M, Bonas S, Dale M. Huntington's Disease: Prevalence and Psychological Indicators of Pain. *Mov Disord Clin Pract*. 2017;4(2):198-204. doi:10.1002/mdc3.12376
- 43. Delussi M, Sciruicchio V, Taurisano P, et al. Lower Prevalence of Chronic Pain in Manifest Huntington's Disease: A Pilot Observational Study. *Brain Sci.* 2022;12(5):676. doi:10.3390/brainsci12050676
- 44. Perrotta A, Serpino C, Cormio C, et al. Abnormal spinal cord pain processing in Huntington's disease. The role of the diffuse noxious inhibitory control. *Clin Neurophysiol*. 2012;123(8):1624-1630. doi:10.1016/j.clinph.2012.01.012
- 45. De Tommaso MC, Serpino C, Difruscolo C, et al. Nociceptive inputs transmission in Huntington 's disease: a study by laser evoked potentials. *Acta Neurol Belg.* 2011;111:33-40. https://pdfs.semanticscholar.org/76f0/c4ef1b84782f56fd9520565114184d7f1335.pdf.
- 46. De Tommaso M, Franco G, Ricci K, Montemurno A, Sciruicchio V. Laser Evoked Potentials in Early and Presymptomatic Huntington's Disease. *Behav Neurol*. 2016;2016:1-8. doi:10.1155/2016/8613729

CHAPTER 1

- 47. Rice ASC, Smith BH, Blyth FM. Pain and the global burden of disease. *Pain*. 2016;157(4):791-796. doi:10.1097/j.pain.000000000000454
- 48. Ferrari AJ, Santomauro DF, Aali A, et al. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990–2021: a systema. *Lancet*. 2024;403(10440):2133-2161. doi:10.1016/S0140-6736(24)00757-8
- 49. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2163-2196. doi:10.1016/S0140-6736(12)61729-2