Huntington's disease: cognition and apathy

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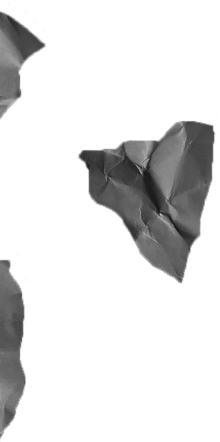

Chapter 1
Introduction

Huntington's disease (HD) is an autosomal, dominant inherited neurodegenerative disorder, characterized by a triad of symptoms including motor abnormalities, behavioral symptoms and cognitive decline[1]. The prevalence of HD varies between regions, in western countries approximately 10 per 100.000 individuals are affected by HD[2]. The mean age of disease onset is between 30 and 50 years of age with a disease duration of 17 to 20 years[1].

In 1872, George Huntington (1850-1916) described the clinical features of, what is now called, Huntington's disease. In his essay 'On Chorea', he already described the hereditary nature, midlife onset, and the clinical symptoms[3]. Roughly 100 years later, in 1983, the huntingtin gene was mapped to the short arm of chromosome 4 which made linkage analysis possible[4]. Ten years later, in 1993, the mutation was identified as an abnormal expansion on the CAG (cytosine, adenine, guanine) trinucleotide on chromosome 4 in the huntingtin gene and genetic testing became an option for individuals at risk[5]. The length of the CAG repeat in the huntingtin gene can be categorized as follows: full penetrance (CAG > 39), reduced penetrance (CAG range 36-39), intermediate penetrance (CAG range 27-35), and normal (CAG < 27). An individual with a full penetrant CAG expansion will develop symptoms at some point in life, however, it cannot be predicted at what age individuals start to develop symptoms[6]. In general, a longer CAG expansion is associated with early disease onset[7].

Clinical symptoms and measurement tools

HD symptoms can be categorized in three domains: motor, cognitive, and behavioral. Motor symptoms are the most recognized signs of HD and typically a clinical diagnosis is determined based on the occurrence of motor symptoms[1, 8]. The most characteristic motor symptom is chorea, unwanted, jerky movements, but other motor symptoms such as dystonia, rigidity, hypokinesia and bradykinesia are also often present. The symptoms worsen over the course of the disease and will eventually interfere with daily activities, such as getting dressed and walking[1]. The Unified Huntington's Disease Rating Scale (UHDRS) was designed to rate the most common symptoms, including motor symptoms, and general functional capacity of daily living of HD expansion gene carriers (HDGEC)[9]. The motor part of the UHDRS is still the gold standard to rate motor abnormalities. This scale ranges from 0 to 124, with higher scores indicating more motor impairment. In research, a cut-off of 5 points on the UHDRS is used to indicate whether HDGECs have substantial motor symptoms; i.e. distinction between pre-motormanifest and motormanifest individuals. The UHDRS has a high inter-rater reliability[9]. Recently, a force transducer, the Q-motor, was developed to be able

to even detect subtle changes in motor performance and was recently used in clinical trials[10].

Cognitive decline is another major HD symptom and was already recognized by George Huntington[3]. The last decades, the cognitive component of HD has been extensively studied, this might partially be ascribed to the fact that cognitive deterioration embodies several cognitive domains which all can be measured with different tools[11]. This is also the challenge to identify the natural course of cognitive decline in HD with diverse studies focusing on different cognitive domains, using different measurement tools, and including different staged HDGECs. It is known that cognitive deterioration can occur before motor symptoms are present and simple psychomotor tasks seem to be sensitive in the period before motor symptoms become present[11-13] whereas tasks of memory and executive functioning appear to become sensitive in the early HD stages[12-14]. Still the exact course of cognitive decline for each domain is still unknown, but finally cognitive deterioration results in dementia in HD[11]. Effort has been made to design cognitive batteries to track cognitive decline in HD and recently the HD cognitive assessment battery (HD-CAB)[15] was designed to track cognitive decline in the early HD phase, i.e. clinically diagnosed HDGECs with still high functional capacity in daily living. However, considering the entire spectrum of the disease, no consensus exists which cognitive tasks should be used in which stage.

Besides motor disturbances and cognitive impairment, behavioral symptoms are more heterogeneously present in HD, as the presence and its severity fluctuates throughout the course of the disease[16, 17]. The most common behavioral symptoms are depressive mood, irritability and apathy[17]. Other symptoms such as hallucinations, delusions and perseverations can also occur. Apathy can already mildly be present in the pre-motormanifest stage[18, 19] and will eventually be severely present in the late stage[16]. It seems that apathy is the only behavioral symptom which worsens as disease progresses, suggesting a neurodegenerative cause, and is negatively related to functional capacity[16, 20]. In addition, apathy and cognitive impairment are also connected. Apathy can occur due to disruption of cognitive processes, i.e. apathy is a result of working memory problems or executive dysfunction[21]. In HD it has been shown that apathy is associated with cognitive decline[22]. Several rating scales have been used in HD to track the behavioral symptoms in HD but only a few are recommended to use in HD as the behavioral symptoms are complex due to co-occurrence of different behavioral symptoms[23]. The Problem Behavior Assessment – short (PBA-s), a semi-structured psychiatric interview, was develop for HD and is now commonly used to rate the presence and severity of the different behavioral symptoms[24].

The last decades, tremendous effort has been made in neuroimaging studies to understand the relationship between HD symptoms and the underlying neurodegenerative process. Magnetic resonance imaging (MRI) technique was often used to map symptoms to structural and/or functional changes in the brain in HD[25]. These studies showed that atrophy of the putamen is correlated to motor symptoms[26,27], atrophy of the caudate is correlated to cognitive deficits[14], and that striatal atrophy already starts before symptoms become apparent[19]. But still a lot is unknown about the development of symptoms and the neurodegenerative process.

As there is no cure of HD, many individuals take medication to manage HD symptoms. In a large European study about 85% received symptomatic treatment, the majority for depression[28]. Unfortunately, there is only low level of evidence on the effects and side effects of medication use in HD and most decision making on prescription is based on clinical practice[29-31].

Aims

As exact knowledge of the course of cognitive decline and the underlying cause of developing apathy is still lacking in HD, the primary aim of this thesis was to gain further insight into the cognitive profile and apathy in Huntington's disease (HD). This information is incredible useful to advice future clinical trials about their design if cognitive decline and/or apathy is targeted.

As HD is a rare disease, research heavily relies on collaboration between HD centers. In 2004, the European Huntington's Disease Network (EHDN) launched the European, multicenter, observational REGISTRY study[32]. We aimed to evaluate whether the most commonly used participant classification makes a useful distinction between HDGECs and whether these groups are homogeneous by giving an overview of the participants' characteristics at the largest REGISTRY HD center (**chapter 2**). Secondly, using the entire European REGISTRY cohort, we aimed to map the cognitive profile in different disease stages, ranging from pre-motormanifest to advanced HD stages, and to evaluate whether CAG length mediates cognitive decline in HD (**chapter 3**). In addition, we explored whether there is a difference in cognitive performance between individuals taking medication targeting non-cognitive neuropsychiatric signs or/and tetrabenazine and non-users in HD (**chapter 4**). The following two chapters focus on apathy, we aimed to relate apathy to the neurodegenerative process in HD (**chapter 5**). In **chapter 6**, we evaluated whether HDGECs and their proxies agree on the degree of apathy by using a self-report questionnaire. General discussion of our findings and future perspectives are outlined in **chapter 7**.

References

1. Roos RA. Huntington's disease: a clinical review. OrphanetJRareDis 2010;5:40.
2. Morrison PJ. Prevalence estimates of Huntington disease in Caucasian populations are gross underestimates. Mov Disord 2012;27:1707-1708.
3. Huntington G. On Chorea. the Medical and Surgical Reporter 1872;26:317-321.
4. Gusella JF, Wexler NS, Conneally PM, et al. A polymorphic DNA marker genetically linked to Huntington's disease. Nature 1983;306:234-238.
5. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. Cell 1993;72:971-983.
6. Novak MJ, Tabrizi SJ. Huntington's disease. Bmj 2010;340:c3109.
7. Sturrock A, Leavitt BR. The clinical and genetic features of Huntington disease. Journal of geriatric psychiatry and neurology 2010;23:243-259.
8. Reilmann R, Leavitt BR, Ross CA. Diagnostic criteria for Huntington's disease based on natural history. Mov Disord 2014;29:1335-1341.
9. Unified Huntington's Disease Rating Scale: reliability and consistency. Huntington Study Group. Mov Disord 1996;11:136-142.
10. Reilmann R, Schubert R. Motor outcome measures in Huntington disease clinical trials. Handb Clin Neurol 2017;144:209-225.
11. Dumas EM, van den Bogaard SJ, Middelkoop HA, Roos RA. A review of cognition in Huntington's disease. Frontiers in bioscience (Scholar edition) 2013;5:1-18.
12. Maroof DA, Gross AL, Brandt J. Modeling longitudinal change in motor and cognitive processing speed in presymptomatic Huntington's disease. JClinExpNeuropsychol 2011;33:901-909.
13. Snowden JS, Craufurd D, Thompson J, Neary D. Psychomotor, executive, and memory function in preclinical Huntington's disease. JClinExpNeuropsychol 2002;24:133-145.
14. Montoya A, Price BH, Menear M, Lepage M. Brain imaging and cognitive dysfunctions in Huntington's disease. JPsychiatry Neurosci 2006;31:21-29.
15. Stout JC, Queller S, Baker KN, et al. HD-CAB: a cognitive assessment battery for clinical trials in Huntington's disease 1,2,3. Mov Disord 2014;29:1281-1288.
16. Thompson JC, Harris J, Sollom AC, et al. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. JNeuropsychiatry ClinNeurosci 2012;24:53-60.
17. van Duijn E, Kingma EM, van der Mast RC. Psychopathology in verified Huntington's disease gene carriers. JNeuropsychiatry ClinNeurosci 2007;19:441-448.
18. Martinez-Horta S, Perez-Perez J, van Duijn E, et al. Neuropsychiatric symptoms are very common in premanifest and early stage Huntington's Disease. Parkinsonism Relat Disord 2016;25:58-64.

19. Tabrizi SJ, Langbehn DR, Leavitt BR, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. Lancet Neurol 2009;8:791-801.
20. Thompson JC, Snowden JS, Craufurd D, Neary D. Behavior in Huntington's disease: dissociating cognition-based and mood-based changes. JNeuropsychiatry ClinNeurosci 2002;14:37-43.
21. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. Cereb Cortex 2006;16:916-928.
22. van Duijn E, Reedeker N, Giltay EJ, Roos RA, van der Mast RC. Correlates of apathy in Huntington's disease. JNeuropsychiatry ClinNeurosci 2010;22:287-294.
23. Mestre TA, van Duijn E, Davis AM, et al. Rating scales for behavioral symptoms in Huntington's disease: Critique and recommendations. Mov Disord 2016;31:1466-1478.
24. Callaghan J, Stopford C, Arran N, et al. Reliability and Factor Structure of the Short Problem Behaviors Assessment for Huntington's Disease (PBA-s) in the TRACK-HD and REGISTRY studies. JNeuropsychiatry ClinNeurosci 2015;27:59-64.
25. Niccolini F, Politis M. Neuroimaging in Huntington's disease. World J Radiol 2014;6:301-312.
26. Aylward EH, Liu D, Nopoulos PC, et al. Striatal volume contributes to the prediction of onset of Huntington disease in incident cases. Biol Psychiatry 2012;71:822-828.
27. Coppen EM, van der Grond J, Roos RAC. Atrophy of the putamen at time of clinical motor onset in Huntington's disease: a 6-year follow-up study. J Clin Mov Disord 2018;5:2.
28. Priller J, Ecker D, Landwehrmeyer B, Craufurd D. A Europe-wide assessment of current medication choices in Huntington's disease. Mov Disord 2008;23:1788.
29. van Duijn E. Treatment of Irritability in Huntington's Disease. Curr Treat Options Neurol 2010;12:424-433.
30. van Duijn E. Medical treatment of behavioral manifestations of Huntington disease. Handb Clin Neurol 2017;144:129-139.
31. Burgunder JM, Guttman M, Perlman S, Goodman N, van Kammen DP, Goodman L. An International Survey-based Algorithm for the Pharmacologic Treatment of Chorea in Huntington's Disease. PLoS Curr 2011;3:RRN1260.
32. Orth M, Handley OJ, Schwenke C, et al. Observing Huntington's disease: the European Huntington's Disease Network's REGISTRY. JNeurolNeurosurgPsychiatry 2011;82:1409-1412.