Huntington's disease : functional and structural biomarkers

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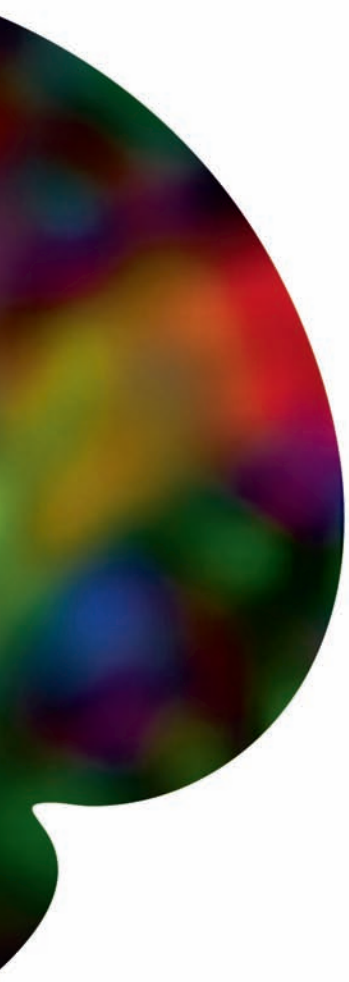

Chapter 1

Introduction

Introduction and aims of the study

Huntington's disease (HD) is an autosomal dominant inherited disease, determined by a mutation in the *Htt* gene coding for the protein Huntingtin. The occurrence of an expansion of the cytosine adenine guanine (CAG) repeat on chromosome 4 leads to destruction of brain neurons[1]. At an unknown point in life, pathogenic processes give rise to gradually progressing disturbance of motor function, cognitive ability, and behaviour. Other symptoms include weight loss and sleep disturbances. Patients typically display the first symptoms between 35 and 45 years of age and die 15 to 20 years later[2].

Genetic testing allows for the identification of individuals that carry the HD gene. A unique research situation arises from the ability to identify individuals who do not show symptoms but will certainly do so in the future. These so called 'premanifest gene carriers' play a valuable role in understanding underlying processes of HD prior to the appearance of symptoms. Commonly, after disease onset, 'manifest' HD patients demonstrate gradual cognitive decline, motor dysfunction and behavioural abnormalities[3]. The occurrence and severity of such symptoms vary per individual, even so, four successive disease stages can be determined. Stages 1 and 2 are classified as 'early HD' and 3 and 4 as 'late stage HD'.[4] The clinical aspects of the disease have been studied extensively since the first description of the disease by George Huntington in 1872[5]. Also, the cellular and tissue changes of HD have been documented. However, this has not resulted in a cure for the disease. Symptom suppression is the only treatment option currently available.

Currently, the complex disease process of HD is not understood. It is not possible to exactly predict how and when symptoms will arise, or how the disease will develop. However, in order to progress towards therapeutic interventions clinical research requires consensus about the measures that could be used to objectively reflect the status and progression of the disease. This thesis focuses on the determination of early biomarkers in premanifest gene carriers and patients with early HD. The identification of one or more suitable biomarkers would allow for future clinical interventions to be accurately monitored.

The ideal biomarker would closely reflect the disease state of HD gene carriers, be non-invasive and objective. All clinical functioning domains have the potential to deliver biomarkers that can meet these criteria. However, due to focus on motor behaviour, cognitive decline was overlooked as an important domain in the HD symptom spectrum for many years. Recently, cognitive deterioration has received more attention[6;7]. This has resulted in the recognition that cognitive deterioration can be part of the course of HD from its earliest disease phase onwards[8]. Diminished executive functioning and psychomotor speed have been shown in premanifest gene carriers[9], however, reports on memory functioning remain inconclusive. In manifest HD memory, psychomotor speed

and executive functioning have been implicated[10]. However, it is unclear which cognitive (sub)domains demonstrate the most consistent deterioration and which areas of cognitive functioning could deliver a cognitive biomarker. Therefore, we aimed to provide an overview of the (sub)domains of cognitive functioning in HD per disease stage, and to indicate which domains have the highest biomarker potential (Chapter 2). Furthermore, we aimed to examine one of the cognitive subdomains to further understand the cognitive process (Chapter 3).

The search for biomarkers extends into the field of brain imaging. The widespread application of magnetic resonance imaging (MRI) has allowed for in vivo exploration of the HD brain[11]. From the first autopsies performed on HD patients in the twentieth century there has been evidence that brain changes are apparent in HD[12]. Especially cell loss in the caudate nucleus and putamen has been observed[13]. The extent of atrophy in the other subcortical grey matter structures in the brain is not well established. Therefore, we aimed to quantify atrophy of the subcortical grey matter structures to determine their involvement in HD pathology (Chapter 4).

Atrophy of the caudate nucleus and putamen has been shown to occur prior to clinical changes. Therefore, atrophy of these regions is a strong candidate biomarker. However, given that cell loss is the final outcome of a sequence of pathological events, it is not unlikely that other changes prior to widespread atrophy could be detected. With this in mind, magnetic resonance spectroscopy (MRS) has been applied in HD, and has demonstrated metabolite disturbances in large brain regions[14]. Quantifying metabolic changes in individual brain structures, especially prior to disease onset, is desirable due to the localised nature of profound brain changes in HD. Application of in vivo MRS has the potential to measure metabolite concentrations present in individual brain structures in HD and thereby give insight into pathofysiological changes. Therefore, we aimed to quantify brain metabolites by applying MRS in subcortical brain structures and to assess the potential of metabolites as biomarkers (Chapter 5).

Inherent structural or functional changes of the subcortical grey matter structures may not be the only cause of their dysfunction in HD. The connectivity of the subcortical structures with other areas of the brain may also play a role in their disturbances. Diffusion tensor imaging (DTI) provides insight into the structural integrity and structural connectivity of brain tissues. DTI has previously been applied to determine the integrity of subcortical structures in HD and has shown diminished integrity of the caudate nucleus, putamen and overall white matter[15;16]. Examining specific white matter pathways to and from brain structures important to HD, may provide further insight into early brain changes. The quantification and integrity of major white matter pathways using DTI in premanifest and early HD is described (Chapter 6).

Autopsy, has shown iron accumulation in the basal ganglia HD brains[17]. The processes and timing of iron accumulation in the course of HD are not fully understood. Furthermore, the relationship between atrophy and iron accumulation has not been examined. Magnetic field inhomogeneities were assessed for quantification of iron levels in premanifest and manifest HD (Chapter 7). Understanding whether excessive iron accumulation is related to cellular loss, or whether this occurs prior to such loss will not only determine the independence of such disease processes but will give insight into iron as a potential biomarker.

In an effort to bridge the gap between the structural brain changes and the functional deterioration, insight is required into the functioning of the brain. Studying potential changes in functional connectivity networks using resting state fMRI, may add to the knowledge of functional changes in HD. We explored the nature and timing of functional disturbances in the HD brain at rest and described the potential of resting state fMRI as a biomarker for HD (Chapter 8).

In the final chapter (Chapter 9) the conclusions are summarised and discussed. Recommendations for future research are given.

References

1. Ross CA, Tabrizi SJ. Huntington's disease: from molecular pathogenesis to clinical treatment. Lancet Neurol 2011;10:83-98
2. Sturrock A, Leavitt BR. The clinical and genetic features of Huntington disease. J Geriatr Psychiatry Neurol 2010;23:243-59
3. Novak MJ, Tabrizi SJ. Huntington's disease: clinical presentation and treatment. Int Rev Neurobiol 2011;98:297-323
4. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979;29:1-3
5. Huntington G. On chorea. George Huntington, M.D. J Neuropsychiatry Clin Neurosci 2003;15:109-12
6. Caine ED, Hunt RD, Weingartner H, et al. Huntington's dementia. Clinical and neuropsychological features. Arch Gen Psychiatry 1978;35:377-84
7. Ho AK, Sahakian BJ, Brown RG, et al. Profile of cognitive progression in early Huntington's disease. Neurology 2003;61:1702-06
8. 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;79:874-80
9. Solomon AC, Stout JC, Weaver M, et al. Ten-year rate of longitudinal change in neurocognitive and motor function in prediagnosis Huntington disease. Mov Disord 2008;23:1830-36
10. Snowden J, Craufurd D, Griffiths H, et al. Longitudinal evaluation of cognitive disorder in Huntington's disease. J Int Neuropsychol Soc 2001;7:33-44
11. Bohanna I, Georgiou-Karistianis N, Hannan AJ, et al. Magnetic resonance imaging as an approach towards identifying neuropathological biomarkers for Huntington's disease.Res Rev. 2008 Jun;58(1):209-25
12. Vonsattel JP, Keller C, Cortes Ramirez EP. Huntington's disease - neuropathology. Handb Clin Neurol 2011;100:83-100
13. Roos RAC, Bots GTAM. Nuclear-Membrane Indentations in Huntingtons-Chorea. Journal of the Neurological Sciences 1983;61:37-47
14. Sanchez-Pernaute R, Garcia-Segura JM, del Barrio AA, et al. Clinical correlation of striatal 1H MRS changes in Huntington's disease. Neurology 1999;53:806-12
15. Rosas HD, Tuch DS, Hevelone ND, et al. Diffusion tensor imaging in presymptomatic and early Huntington's disease: Selective white matter pathology and its relationship to clinical measures. Mov Disord 2006;21:1317-25
16. Reading SA, Yassa MA, Bakker A, et al. Regional white matter change in pre-symptomatic Huntington's disease: a diffusion tensor imaging study. Psychiatry Res 2005;140:55-62
17. Chen JC, Hardy PA, Kucharczyk W, et al. MR of human postmortem brain tissue: correlative study between T2 and assays of iron and ferritin in Parkinson and Huntington disease. AJNR Am J Neuroradiol 1993;14:275-81