Premanifest Huntington's disease : a study of early biomarkers

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Chapter 1

General introduction

Huntington's disease (HD) is an autosomal dominantly inherited, neurodegenerative disease characterised by disorders of movement, cognition and behaviour. The genetic defect causing HD is an abnormal CAG expansion in the gene that codes for the protein, huntingtin, on chromosome 4.[1] In healthy individuals the number of CAG repeats is less than 27; the presence of 36 or more repeats indicates that the individual will develop HD. By means of predictive testing, individuals at risk of inheriting the mutation can be identified prior to the disease becoming clinically manifest. The length of the CAG repeat explains 50-70% of the variability in clinical onset age, a greater number of repeats tending to result in earlier age at onset.[2] The mean age at symptom onset is in the mid-40's and the mean disease duration ranges between 15 and 20 years.[3] In The Netherlands, the number of HD patients is estimated at 1,200-1,500 and approximately 6,000-9,000 individuals are at risk. Slightly less than half of the at-risk carriers carry the HD mutation and will eventually develop HD.

Through different mechanisms, the abnormal huntingtin is believed to promote neuronal cell death and dysfunction in a variety of brain regions, particularly the basal ganglia. The most striking neuropathological changes are found in the caudate nucleus and the putamen, but other subcortical and cortical regions of the brain also exhibit neuronal loss.[4-6] HD neuropathology leads in particular to disruption of cortical-basal ganglia brain circuits involved in motor, cognitive and behavioural processes.[7] At present, many symptomatic treatments are available but there are as yet no means of preventing, slowing down or curing HD.

The major motor disturbance in HD is the presence of unwanted choreatic movements. Oculomotor abnormalities and impaired voluntary movements are also among the earliest signs and are present in the vast majority of patients.[1] Bradykinesia and rigidity often dominate the late stages of disease. Cognitive deterioration is a second key feature of HD and is characterised by memory dysfunction, executive dysfunction, impaired psychomotor skills, and attention deficits.[1,8] Behavioural symptoms associated with HD are more variable in their expression than the motor and cognitive changes and do not follow the same progressive course. Common symptoms are a depressed mood, anxiety, irritability, and apathy.[9,10] Although motor disturbances severely debilitate the patient, cognitive and behavioural changes are often reported to be more distressing for both patients and caregivers.

The clinical diagnosis of manifest HD is generally based on the appearance of unequivocal motor signs identified by a neurologist, along with a positive family history and confirmation by DNA-testing. However, it is well recognised that there is great variation in the age at onset of clinical signs, the initial sign presentation, the clinical course of HD, and the duration of illness. Accumulating research supports a premanifest phase, during which symptoms and signs gradually appear and progress until a definite diagnosis can be made based on neurological examination.

In the search for a causal treatment of HD, there is an urgent need for objective measures that provide more insight into early clinical alterations and morphological and neurophysiological brain changes in HD. Although the genetic mutation serves as a trait marker, it provides no information

on the disease state. A better understanding of the phenoconversion phase from premanifest to manifest HD is, therefore, critical.

Premanifest Huntington's disease

Patients and/or relatives often report symptoms before they reach a point where the disease becomes manifest and a medical specialist confirms the diagnosis. The availability of the genetic test has made it possible to study changes in the premanifest phase of HD. Results from cross-sectional studies in gene-tested, premanifest carriers (described hereafter as carriers) showed that subtle motor, cognitive and behavioural abnormalities can be demonstrated before the onset of unequivocal motor signs. Some studies showed abnormalities in motor functioning in carriers, e.g. oculomotor, functional motor and psychomotor slowing.[11,12] Others found that on cognitive functioning tests, carriers perform worse than non-carriers. Impaired cognitive domains include: intelligence indices, diverse aspects of memory, visuoconstruction, psychomotor and executive skills.[13-15] Furthermore, premanifest behavioural and personality changes have been described and include depressive mood, irritability and aggressive behaviour.[10,16,17]
Longitudinal studies have provided the possibility of finding out whether measures that prove sensitive in detecting premanifest abnormalities can also demonstrate a decline over time, and be used to monitor whether carriers approaching clinical disease onset display abnormalities in specific areas. Follow-up designs show discrepant results. Some studies, varying in follow-up period from 2 to 4 years, could not demonstrate changes in motor and cognitive functioning in carriers compared to non-carriers.[18-20] Others found changes over the years (1 to 10 years) in motor functioning, psychomotor speed, executive functioning, attention and memory.[21-25] Discrepancies between findings in premanifest studies are often attributed to heterogeneity in time to onset, variation in sample size, differing strictness of inclusion criteria for the presence of motor signs and diversity in follow-up periods. Furthermore, there is inconsistency in the comprehensiveness of the used neuropsychological test batteries. For example the study with the most extended follow-up period did not include memory tasks,[25] whereas psychomotor and executive tests are included almost consistently. Additional longitudinal studies with a comprehensive test battery and lengthy follow-up period should give more insight into the tasks most sensitive to tracking clinical decline in the premanifest phase and to determining whether clinical instruments are useful for monitoring future therapeutic trials.

Detecting clinical deterioration before the onset of unequivocal motor signs has prompted research into understanding the nature of neuropathological changes in premanifest HD. Brain imaging tools enable to observe ongoing pathological processes in vivo and to examine associations with the evolution of clinical characteristics.

MRI in Huntington's disease

Magnetic Resonance Imaging (MRI) is a widely available, non-invasive tool allowing the visualisation of the brain in vivo with high spatial resolution and the opportunity to quantify brain parameters.

Atrophy of the striatum (caudate nucleus and putamen) on MRI is a well-known marker for manifest HD and has been linked to motor impairment and cognitive deficits.[26,27] Structural changes in manifest HD have also been demonstrated in other subcortical (e.g. globus pallidus, thalamus) and cortical regions. White matter atrophy and smaller thalamus volume were associated with worse cognitive functioning, emphasising the contribution of extra-striatal abnormalities in the phenotype of HD.[28,29]
Volumetric studies in premanifest carriers showed significant striatal atrophy many years prior to manifest HD.[30-33] Atrophy becomes more severe as clinical disease onset approaches.[32] Extra-striatal volume reductions in the globus pallidus and thalamus were also reported, but were found to begin later.[34] Recent Voxel Based Morphometry (VBM), Diffusion Tensor Imaging (DTI) and Positron Emission Tomography (PET) studies have also demonstrated sensitivity for premanifest subcortical and cortical changes.[35-39] Furthermore, early white matter volume loss, cortical thinning and grey matter abnormalities have been demonstrated.[32,37,40] Relatively few studies focused on associations between structural abnormalities and clinical functions in premanifest HD. Smaller striatal volume has been linked to subtle motor abnormalities,[31,41,42] worse psychomotor performance[31] and lower scores on a verbal episodic memory task.[31,43] Quantitative MRI techniques may further improve our understanding of how regional and diffuse brain changes in HD develop and how these are related to the genotype and heterogeneous phenotype of HD.

EEG in Huntington's disease

Electroencephalography (EEG) is used to record the electrical brain activity. It is a cost-effective, non-invasive tool, sensitive to functional brain changes. In contrast with MRI, EEG has high temporal but low spatial resolution. Neurodegenerative disease and dementia have been associated with slow EEG activity.[44] While many recent studies have focused on MRI techniques in HD, comparatively fewer have utilised electrophysiological measures. In patients with HD, EEG abnormalities consist of increased theta and reduced alpha power.[44,45] In mild to moderate HD, decreased global alpha and frontal theta power and increased global delta and beta power were demonstrated and were found to be associated with motor and cognitive impairment.[46] Only one study focused on EEG in premanifest HD carriers and found that alpha activity was reduced, specifically in individuals near clinical onset age.[45] In most clinical EEG studies registration is limited to standard conditions. In EEG studies of the continuum of cognitive decline, it was shown that cognitive challenging during EEG revealed abnormalities in Mild Cognitive Impairment (MCI), while conventional EEG conditions did not.[47] As neuropsychological studies have described subtle abnormalities in executive functioning and memory in premanifest carriers, EEG combined with memory or executive tests might reveal early changes in brain functioning in HD before clinical signs become overt.

Another potentially useful electrophysiological technique for the detailed analysis of HD-related neuronal and cognitive deterioration is the recording of Event-Related Potentials (ERP). The ERP provides information on the efficiency of stimulus processing, which depends mainly on the integrity of complex functional neuronal circuits. The P3 is the most extensively studied ERP.

The P3 is a positive, large amplitude potential with a typical peak latency between 300 and 500 ms, and is elicited in response to deviant stimuli in simple auditory or visual discrimination tasks. The amplitude of the P3 reflects attention to stimulus information when representations are updated.[48] The P3 latency is considered as stimulus classification speed and is sensitive to task processing demands and cognitive abilities. P3 abnormalities have been shown in HD patients as well as premanifest carriers. Studies with auditory and visual oddball paradigms, showed an increased P3 latency in both patients and carriers, while the P3 amplitude was altered in patients only.[49,50] In contrast, a study by de Tommaso et al. showed that P3 latency was within the normal range in most HD patients and in all carriers.[51] The P3 has also been used to examine processes related to inhibition in Go/No-go paradigms. Beste et al. showed a strongly decreased P3 amplitude during No-go trials in HD patients and showed an association with higher CAG repeat length.[52]
Interestingly, the P3 is reported to be partly generated by the basal ganglia.[53] Since degeneration of these brain structures starts many years before clinical disease onset, studying the interplay between P3 and basal ganglia in premanifest HD would lead to new insights into the disease process.

Outline of the thesis

Objective measures, also called biomarkers, that provide more insight into early clinical abnormalities and morphological and neurophysiological brain alterations in HD need to be identified. They should contribute to the early detection of change, the development of neuroprotective agents, and to the monitoring of disease progression and treatment. In addition they should help in the establishment of better criteria for the definition of onset for clinical practice.

The general objective of this thesis was, therefore, to investigate whether early clinical alterations and structural and functional brain markers could be detected in carriers of the HD gene who are still without manifest motor signs. Furthermore we investigated associations between clinical measures and several quantitative MRI and EEG markers.

First of all, we aimed to detect brain deficits using MRI before carriers of the HD gene showed clinical manifest signs of HD. Therefore, volumetric MRI (chapter 2), Magnetisation Transfer Imaging (MTI) (chapter 3) and basal ganglia hypointensities on T2-weighted scans (chapter 4) were compared between carriers and non-carriers. Furthermore, we reported whether these measurements could be associated with phenotypical and genotypical characteristics in carriers.

The second aim was to investigate whether EEG parameters during cognitive challenging would reveal abnormalities in brain functioning in premanifest HD. EEG activity during memory activation was studied in carriers compared to non-carriers (chapter 5). Furthermore we analysed P3 ERP during a Go/No-go sustained attention task and we described the relation with basal ganglia volumes in carriers of the HD gene (chapter 6).

Thirdly, we aimed to learn more about the presence of subtle motor, cognitive and behavioural abnormalities in premanifest HD and about the successive development of clinical symptoms of HD after a 7- year follow-up (chapter 7 and chapter 8).

The main conclusions are discussed (chapter 9).

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