Premanifest Huntington's disease : a study of early biomarkers

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Summary

Huntington's disease (HD) is an inherited neurodegenerative disease that becomes manifest in midlife and is characterised by progressive motor, cognitive and behavioural dysfunction.[1] Although the clinical diagnosis of HD is usually based on the first appearance of motor signs, a positive family history and confirmation by DNA-testing, subtle clinical changes in motor function, cognition and behaviour are known to precede overt disease manifestation.[2-4] Furthermore, early changes in brain structure and function have been demonstrated in the premanifest phase of HD.[5-9]

Objective 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, to the development of neuroprotective agents, and to the monitoring of disease progression and treatment. In addition they should help to establish 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 functional and structural 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.

Detecting brain abnormalities in premanifest HD using different MRI methods

Quantitative MRI neuroimaging techniques provide the possibility of developing instruments suitable for detecting and monitoring brain changes in carriers before motor signs become manifest. In **chapter 2** we assessed whether premanifest basal ganglia alterations could be demonstrated using manual segmentation of basal ganglia on T1-weighted MRI scans. We examined volumes of the caudate nucleus, putamen, globus pallidus and thalamus. Furthermore, motor, cognitive and behavioural functioning were assessed using the Unified Huntington's Disease rating Scale (UHDRS). Sixteen carriers without manifest motor signs were compared to 14 non-carriers. The results showed that volumes of the caudate nucleus, putamen and globus pallidus were significantly smaller in carriers than in non-carriers while no differences between groups were found on clinical evaluation. In carriers, a smaller globus pallidus volume was associated with more motor abnormalities. Also, a smaller putamen volume correlated with poorer psychomotor function. These results suggest that motor and psychomotor measurements may be suitable clinical markers for future neuroprotective trials when combined with volumetric imaging.[10]

Magnetisation Transfer Imaging (MTI) proved to be sensitive to the first microstructural brain changes in different neurodegenerative disorders, like Alzheimer's disease and Parkinson's disease, even before volumetric alterations.[11-14] In **chapter 3**, we addressed whether diffuse brain abnormalities, as detected by MTI, are present in premanifest HD carriers. Magnetisation transfer ratio histograms of the whole brain, grey matter and white matter were compared between carriers and non-carriers and were associated with clinical measures and CAG repeat length. A lower MTR peak height was associated with more UHDRS motor abnormalities and with a longer CAG repeat length. These data show that although we could not demonstrate altered MTI characteristics in premanifest HD, we did demonstrate that the MTR peak height reflects genetic and subclinical disease status and may be of value in monitoring further disease progression and provide insight into clinical heterogeneity.[15]

Brain iron accumulation has been proposed as an important factor in the pathogenesis of neurodegenerative diseases and has been associated with MRI T2-weighted hypointensities.[16-21] **Chapter 4** reported on our exploratory study into whether the degree of hypointensities in the basal ganglia of premanifest carriers differs from non-carriers. Using an innovative quantitative method developed by Philips research, we classified each pixel in the basal ganglia as hypointense or not, resulting in a total number of hypointense pixels for each individual. Carriers showed an increased amount of hypointensities in the basal ganglia compared to non-carriers, specifically in the globus pallidus. A greater number of hypointensities was furthermore strongly related to more UHDRS motor abnormalities, a longer CAG repeat length and being closer to estimated disease onset. These preliminary results indicate that excessive iron deposition may be present in premanifest HD and could play a role in early neuropathology of HD. Hypointensities in the basal ganglia may therefore be considered a biomarker for HD.[22]

Brain functioning during cognitive challenge in premanifest HD

EEG provides the possibility of measuring functional changes as a response to altered brain morphology. 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.[23] In **chapter 5** we investigated whether the EEG during memory activation revealed abnormalities in premanifest HD. To this end, 16 carriers and 13 non-carriers of the HD gene were evaluated using neurological, neuropsychological and EEG investigations. The EEG was registered during rest, eyes closed and memory activation. The EEG during memory activation showed less relative and less absolute alpha power in carriers compared to non-carriers, even though memory performance was similar. No associations were found with phenotypical or genotypical characteristics. It was concluded that memory activation revealed functional brain changes in HD before clinical signs become manifest.[24]

In **chapter 6** we studied P3 Event-Related Potential (ERP) during the Sustained Attention to Response Task (SART), a Go/No-go task sensitive to attentional problems. The P3 is used to investigate the neuronal basis of cognitive changes and is presumably partly generated by the basal ganglia. We assessed whether altered P3 components were present in premanifest HD and we were especially interested in a possible association with basal ganglia volumes. In carriers we demonstrated exceptionally strong associations of longer P3 latency with smaller corpus striatum volume, a higher CAG repeat length and more motor abnormalities. P3 amplitude and latency themselves or attentional performance on the SART did not differ between carriers and non-carriers. These results

suggest that a combination of structural brain assessments and P3 may be an effective and quite sensitive measure for evaluating therapeutic strategies and may provide insight into the structural abnormalities that underlie changing P3 characteristics.

Premanifest motor, cognitive and behavioural functioning

Finding suitable tools to capture early clinical HD signs is important for measuring clinical deterioration or improvement (e.g. for therapeutic trials), insight into disease for better management of carriers and relatives and better criteria for the definition of onset. In **chapter 7** we examined relations between motor functioning, cognitive functioning and mood and behavioural characteristics in 34 HD patients, 46 premanifest carriers and 88 non-carriers. Our main aim was to investigate whether associations found in patients were already present in the premanifest phase of HD. We showed that patients were significantly impaired compared to carriers and non-carriers in all investigated domains. In the patient group, disease duration was associated with chorea, while functional capacity correlated specifically with voluntary movements, cognitive functioning and psychomotor speed. In carriers, functional capacity was strongly related to behavioural functioning. Cognitive and motor functioning correlated equally with psychomotor speed in both patients and carriers. These findings demonstrate that psychomotor speed is a key feature in (early) HD. A parallel evolution of specific motor disturbances occurred with specific cognitive deficits, whereas behavioural changes seemed more variable.

Longitudinal studies have provided the possibility of finding out whether measures that prove to be sensitive in detecting premanifest abnormalities also show a decline over time, and monitor whether carriers approaching clinical disease onset display abnormalities on specific domains. **Chapter 8** described a longitudinal study in which we investigated how motor, cognitive and behavioural functioning changed over a period of seven years in premanifest carriers compared to non-carriers. Twenty-nine carriers and 43 non-carriers were assessed four times with the UHDRS and an extensive neuropsychological test battery. Carriers performed consistently worse on executive function (Symbol Digit Modalities Test (SDMT), Stroop colour word test, Trail making Test (TMT) and WAIS-R arithmetic). Over the years, carriers showed a decline on memory and concentration function (Wechsler Memory Scale (WMS) and in motor function (UHDRS motor scale). Changes over time could especially be ascribed to carriers converting to manifest HD during follow-up. We concluded that standardised motor assessments and objective memory and concentration tasks are sensitive to change over a period of 7 years, specifically in carriers converting to manifest HD. Executive tasks also showed subtle cognitive abnormalities in premanifest HD, but a decline over time could not be demonstrated on these tasks. Because of discrepancies between studies and the discontinuous evolvement of clinical changes, uniformity in international research through multi-site collaborative research models will improve premanifest HD research substantially and point to a selection of specific clinical measures sensitive to change in premanifest HD.

In **chapter 9**, scientific and clinical implications of the key findings are discussed.

References

1. Bates G, Harper PS, Jones L. Huntington's disease. Third ed.: Oxford University Press, 2002
2. Kirkwood SC, Siemers E, Bond C et al. Confirmation of subtle motor changes among presymptomatic carriers of the Huntington disease gene. Arch Neurol. 2000; 57:1040-1044
3. van Duijn E, Kingma EM, van der Mast RC. Psychopathology in verified Huntington's disease gene carriers. J Neuropsychiatry Clin Neurosci. 2007; 19:441-448
4. Witjes-Ané MNW, Vegter-van der Vlis M, van Vugt JPP et al. Cognitive and motor functioning in gene carriers for Huntington's disease: A baseline study. Journal of Neuropsychiatry and Clinical Neurosciences. 2003; 15:7-16
5. Aylward EH, Sparks BF, Field KM et al. Onset and rate of striatal atrophy in preclinical Huntington disease. Neurology. 2004; 63:66-72
6. de Tommaso M, De Carlo F, Difruscolo O et al. Detection of subclinical brain electrical activity changes in Huntington's disease using artificial neural networks. Clinical Neurophysiology. 2003; 114:1237-1245
7. Hömberg V, Hefter H, Granseyer G et al. Event-related potentials in patients with Huntington's disease and relatives at risk in relation to detailed psychometry. Electroencephalography and Clinical Neurophysiology. 1986; 63:552-569
8. Paulsen JS, Magnotta VA, Mikos AE et al. Brain structure in preclinical Huntington's disease. Biological Psychiatry. 2006; 59:57-63
9. Rosenberg C, Nudleman K, and Starr A. Cognitive evoked potentials (P300) in early Huntington's disease. Arch Neurol. 42[10], 984-987. 1985.
10. Jurgens CK, van de Wiel L, van Es AC et al. Basal ganglia volume and clinical correlates in 'preclinical' Huntington's disease. J Neurol. 2008; 255:1785-1791
11. Anik Y, Iseri P, Demirci A et al. Magnetization transfer ratio in early period of Parkinson disease. Academic Radiology. 2007; 14:189-192
12. Tambasco N, Pelliccioli GP, Chiarini P et al. Magnetization transfer changes of grey and white matter in Parkinson's disease. Neuroradiology. 2003; 45:224-230
13. van der Flier WM, van den Heuvel DM, Weverling-Rijnsburger AW et al. Magnetization transfer imaging in normal aging, mild cognitive impairment, and Alzheimer's disease. Ann Neurol. 2002; 52:62-67
14. van Es AC, van der Flier WM, Admiraal-Behloul F et al. Magnetization transfer imaging of gray and white matter in mild cognitive impairment and Alzheimer's disease. Neurobiol Aging. 2006; 27:1757-1762
15. Jurgens CK, Bos R, Luyendijk J et al. Magnetization transfer imaging in 'premanifest' Huntington's disease. J Neurol. 2010; 257:426-432
16. Dexter DT, Carayon A, Javoy-Agid F et al. Alterations in the levels of iron, ferritin and other trace metals in Parkinson's disease and other neurodegenerative diseases affecting the basal ganglia. Brain. 1991; 114 (Pt 4):1953-1975
17. Gotz ME, Double K, Gerlach M et al. The relevance of iron in the pathogenesis of Parkinson's disease. Ann N Y Acad Sci. 2004; 1012:193-208
18. Zecca L, Youdim MB, Riederer P et al. Iron, brain ageing and neurodegenerative disorders. Nat Rev Neurosci. 2004; 5:863-873

19. Drayer B, Burger P, Darwin R et al. MRI of brain iron. AJR Am J Roentgenol. 1986; 147:103-110
20. Haacke EM, Cheng NY, House MJ et al. Imaging iron stores in the brain using magnetic resonance imaging. Magn Reson Imaging. 2005; 23:1-25
21. Schenker C, Meier D, Wichmann W et al. Age distribution and iron dependency of the T2 relaxation time in the globus pallidus and putamen. Neuroradiology. 1993; 35:119-124
22. Jurgens CK, Jasinschi R, Ekin A et al. MRI T2 Hypointensities in basal ganglia of premanifest Huntington's disease. PLoS Curr. 2010; Sep 2; 2.
23. van der Hiele K, Vein AA, Kramer CGS et al. Memory activation enhances EEG abnormality in mild cognitive impairment. Neurobiol Aging 2007; 28(1):85-90.
24. van der Hiele K, Jurgens CK, Vein AA et al. Memory activation reveals abnormal EEG in preclinical Huntington's disease. Mov Disord. 2007; 22:690-695