Premanifest Huntington's disease : a study of early biomarkers

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Chapter 9

Discussion and future perspectives

In this study, we looked for measures that might be considered as biomarkers in premanifest Huntington's disease (HD). Objective and sensitive markers are needed to gain insight into early neuropathological processes, to improve early detection of the conversion to manifest disease when disease modifying therapies are likely to be most effective, to monitor disease progression, and detect efficacy of therapeutic interventions. In addition they should help in the establishment of better criteria for the definition of onset for clinical practice.

Scientific implications

Quantitative MRI measures as a biomarker in premanifest HD

First, we showed that quantitative MRI measures enable brain abnormalities to be demonstrated before carriers of the HD gene show manifest disease signs. This study confirms that a decrease in basal ganglia volume predates clinical diagnosis by many years and is a sensitive marker in premanifest HD.[1-3] It is, however, a matter of debate whether basal ganglia atrophy progresses slowly from birth,[4] or whether neurodegeneration begins later in life with progression to manifest HD in just a few years.[5] Aylward et al. suggested that significant striatal atrophy begins around 11 years prior to onset of clinical disease signs, which is important for the timing of implementing neuroprotective therapy before atrophy is well underway.[6] The evidence we provided for white matter atrophy in premanifest carriers emphasises the importance of also including extra-basal ganglia structures when tracking premanifest HD. A recent cross-sectional study confirmed reduced white matter volume even far from estimated clinical disease onset.[3] Since treatment may have unwanted secondary effects and/or be expensive and therapeutic efficacy should be detected over short periods, a biomarker specific for the phase close to onset might be a more preferable surrogate marker in monitoring clinical trials. Presumably, at some point additional factors trigger an acceleration of the neuropathological process. In our explorative study we provided evidence that excessive iron accumulation might be an important factor in premanifest basal ganglia damage. The strong association with proximity to clinical disease onset indicates that this finding might be very specific for the phenoconversion phase and could serve as an important starting-point for therapeutic trials. Hypothetical, brain iron chelating therapy might be monitored with MRI T2-hypointensity quantification and might result in reduced iron accumulation in the basal ganglia and ideally, delayed clinical onset. Also, the easy to administer MRI technique makes iron accumulation an interesting innovative candidate marker.

Overall, the MRI measures applied in this study will be useful for measurement of progression since imaging can be repeated over time and may provide objective and precise measures of change. However, in contrast to volumetric MRI, other MRI applications, like Diffusion Tensor Imaging (DTI), Positron Emission Tomography (PET), MR spectroscopy (MRS) and functional MRI (fMRI) may shed more light on the underlying microstructural and connectivity alterations, abnormalities in metabolism and receptor distribution, and abnormalities in brain activity in premanifest HD.[7,8] Since different imaging techniques can detect early markers in premanifest HD an integrative multimodal imaging approach seems necessary to show whether a combination of imaging techniques is superior to a single substrate approach.[9] Furthermore, the involvement of multiple

brain abnormalities in premanifest HD suggests that pharmacological therapy should be aimed at multiple disease mechanisms.

Second, the associations we found between quantitative MRI measures and clinical characteristics indicate that these markers may predict current and future clinical function and may serve as endpoints for clinical trials. We expanded on previous MRI findings by demonstrating that smaller basal ganglia volumes were associated with worse motor and cognitive functioning in premanifest HD suggesting that a combination of these measures can predict who will convert to manifest HD within a certain time frame. Although Magnetisation Transfer Imaging (MTI) did not prove to be a sensitive marker for early brain deficits, it showed strong associations with CAG repeat expansion and subtle motor abnormalities. Combining MRI and clinical measures in longitudinal studies will be suitable for monitoring the contribution of different kinds of pathological processes to the changing phenotype. The ongoing international multi-centre (Leiden, London, Paris, Vancouver), multidisciplinary TRACK-HD study is an important example in improving research on the subject.[10] Also, longitudinal data from the PREDICT-HD study will become available in the near future and will contribute substantially to the knowledge on the combined value of measures in the phase of onset of HD.[3,11] Eventually, hope is focused on finding a combination of biomarkers that changes in response to treatments which delay the onset of clinical signs and also reduce symptoms.

EEG measures as a biomarker in HD

EEG has the advantage that direct associations between brain and function can be studied with high temporal resolution. This method is not often used in HD research, probably because extra care should be taken to limit the amount of EEG contamination due to electromyographic artefacts, such as blinks and eye movements. Also, individuals using psychotropic medication are excluded because this is known to affect the EEG. By careful selection of EEG samples and analysis of the frequency bands with least susceptibility to motor artefacts, with a view to future studies on manifest HD, we demonstrated the suitability in premanifest HD of our simple, widely available EEG procedures.

The few findings obtained with EEG in HD research are based on conventional EEG conditions such as rest, eyes closed and eyes open. This study showed that when using memory activation during EEG registration early functional brain changes, reflected in reduced alpha power, could be demonstrated in premanifest HD. This was the only brain measure that we could not relate to the HD genotype or the phenotype, which raised the possibility that this phenomenon is a trait marker of underlying developmental brain differences between groups, rather than a state marker. However, it may be that the finding is very specific for working memory and predates alterations in memory function as found in our longitudinal clinical study in premanifest HD. Memory function in HD may then depend on factors other than those studied here. Alternative cognitive paradigms, such as executive function, may be useful in the further study of functional brain changes using EEG in premanifest HD. Remarkably strong associations could be demonstrated between the P3 Event-Related Potential and motor function, basal ganglia volumes and CAG repeat length. This indicates that P3 differences between groups may become apparent during phenoconversion and prove sensitive to change.

It is of interest to study if the associations between the P3 and basal ganglia structures are specific for the used Go/No-go paradigm of the SART or point to a general involvement of basal ganglia in P3 generation. Especially, since response inhibition has been found to depend on basal ganglia-prefrontal interactions.[12,13]

With the EEG and ERP study we demonstrated the applicability and value of electrophysiological measures in premanifest HD. A recent review by Nguyen et al. (2010) integrates key electrophysiological findings in HD and gives valuable recommendations for further research on this matter.[14] Although we do not believe that the EEG should be used as a single diagnostic marker, the presented EEG techniques might be considered for therapeutic trials since functional brain measures will probably be more sensitive for drug-related changes in future disease modifying trials than morphological brain measures.
A combination of measurements, such as EEG and structural MRI, might be useful for determining a 'risk profile' of carriers who are more likely to show decline in the near future and progress to manifest HD. To overcome the limitations of EEG and ERP concerning source localisation a new approach using the combination of functional Magnetic Resonance Imaging (fMRI) with simultaneously acquired EEG and ERP might enhance important imformation.[14,15]

Clinical measures as a biomarker in HD
Clinical measures are attractive as biomarkers since they are easy to assess and are valuable as a marker of symptomatic benefit in therapeutic trials (clinical endpoints). The UHDRS cognitive section has been the basis for most neuropsychological test batteries in premanifest studies and includes exclusively timed executive tasks, focusing on psychomotor speed and cognitive flexibility. We confirmed that psychomotor tasks are a key feature in characterising HD, even long before the onset of clinical signs. However, because of the occurrence of practice effects, they seem less suitable for tracking short intervals in therapeutic trials in premanifest HD. Findings from our longitudinal study on clinical markers and the study on cognitive challenging during EEG emphasise the importance of including memory tasks for neuropsychological evaluation in research in a standard manner.
Although there is a lot of speculation about the usefulness of the UHDRS motor section in scientific research, we demonstrated a significant decline in motor functioning of carriers over the years using this scale. Furthermore, UHDRS motor scores showed strong associations with several brain characteristics indicating that this measure might be a good reflection of brain functioning and, therefore, a monitor of HD-related change. The debated inter- and intra-rater reliability of the UHDRS motor scale will probably improve over the coming years since many neurologists involved in HD are reaching a consensus regarding motor examination within the European Huntington's Disease Network (EHDN).[16] Current studies including more objective motor assessments, such as tongue force variability or self-paced tapping, will provide additional quantitative instruments.[10] Overall, clinical changes could only be detected after an extended follow-up period, probably because the group studied included many individuals in whom onset was a long way off. For therapeutic trials, it would be preferable to select individuals close to onset based on time to onset estimations.[17]

Clinical implications

A clinical diagnosis of HD is in general still based on the unequivocal presence of HD motor signs recognised by a neurologist in the context of a family history of HD and confirmed with an elongated CAG repeat in DNA analysis. For the neurologist, the UHDRS motor section is the standard for the motor examination. In our follow-up study we confirmed that a decline could be found on this motor scale in carriers converting to manifest HD. Furthermore, we extended previous studies demonstrating that cognitive changes are also part of the premanifest phase. We showed that besides executive tasks, memory and concentration tasks should be included in a standard manner when evaluating cognitive functioning in premanifest HD. Family members also report changes in motor functioning, cognition, behaviour and daily activities prior to clinical diagnosis.[18] It has been shown that one of their major concerns is the lack of information about premanifest HD and the difficulty in understanding changes which may represent early stages of HD.[18] These findings emphasise the need for re-examining the criteria for a clinical diagnosis and the requirement of management for family members and the individual with premanifest HD in the phase before traditional clinical signs become manifest.

The findings from our correlational MRI–clinical studies indicate that combining these measurements for a clinical purpose in the premanifest phase might be of value. Baseline assessment in carriers, including motor evaluation, neuropsychological assessment, psychiatric assessment, and MRI scan might help in the timing of clinical diagnosis and the counselling process when at some point carriers and family members mention symptoms. The announcement of a clinical diagnosis of HD changes the status of a gene carrier with subjective health to being a patient. On the one hand, it seems important that carriers function normally for as long as possible without the burden of disease signs; on the other hand, timely adaptation to the limitations is necessary. Early detection of change might prevent carriers withdrawing from employment and social activities when indefinable complaints emerge. It might also contribute to early adaptation of work activities, longer participation in society and prolongation of financial independence.
A multidisciplinary approach may help in finding a balance between the positive and negative implications of a diagnosis in an early phase of HD and contribute to improved individual care and treatment plans. A multidisciplinary team and extensive international guidelines are already standard for the phase of genetic testing and evaluate the pre-test psychological and physical well being and consequences of the genetic test.[19] Although behavioural complaints vary between HD carriers, psychosocial support should be readily available not only during the genetic testing phase, but also as part of this premanifest multidisciplinary care since we showed that more behavioural complaints in carriers without motor signs are associated with a worse impact on daily functioning. Overall, better care strategies should alleviate the burden for patients, carriers and their caregivers. Furthermore, tighter criteria for premanifest HD used more uniformly in clinical practice and research as part of a multidisciplinary approach will enable better identification of subgroups at high risk of developing manifest HD within a certain time frame. In The Netherlands, however, only a quarter of the risk carriers decide to undertake the predictive test, mainly since no prevention

or treatment is available. Predictive testing has clear benefits but the possible test outcomes also have significant psychological and social implications for future life courses.[20] Uncertainty is the main reason for undertaking the genetic test; but when the mean onset age approaches or the first subjective changes are detected, uncertainty will again rise about the possibility that the disease has started.[21] Combining clinical and technical measures as biomarkers would enable to improve prediction of age at onset and disease progression and remove some of this uncertainty. It is however expected that the uptake of the genetic test will probable not increase until significant treatment is available.

Comments

Strengths of the presented studies include the quantitative nature and reliability of the MRI and EEG methods used. Manual tracing of the basal ganglia structures showed high inter-rater reliability. Furthermore, we used only a small set of easily available EEG parameters that cannot be overly affected by recording problems, to ensure clinical applicability. Also, the diversity of brain characteristics measured and the extensive clinical aspects evaluated, including a broad neuropsychological assessment, implies that important future directions for research can be derived from the findings in this study.

Some limitations of the presented studies should be mentioned. There is considerable variability in the methods used in MRI and EEG research into HD. This makes it hard to compare our findings with the literature. Also, not all of the applied MRI techniques are widely available. The study sample of the MRI and EEG projects is relatively small because of the explorative approach. Furthermore, group heterogeneity, i.e. combining participants close to clinical disease onset and those far from onset in a single sample, may lead to mixed results. Also, the sensitivity of the MRI and EEG measures to longitudinal change has not been evaluated, but they are currently being applied. A limitation to studying clinical measures is that they are susceptible to practice and motivational effects and show a bias towards individuals who are genetically tested and compliant into participating in these studies. Study drop-outs proved to have worse baseline performances in our longitudinal study and may have contributed to slightly distorted outcomes.[22]

Future perspectives

Findings of the present study point to the importance of studying a combination of biomarkers in premanifest HD. We advocate a multifactorial approach with simultaneous assessment of combinations of various MRI, EEG and clinical measures with respect to diagnosis and prognosis of future clinical decline. Differing biomarkers will probably be needed to follow change with time, to detect specific phenoconversion or to track therapeutic effects. Longitudinal designs and follow-up of the current cohorts are necessary to determine the validity, reliability, feasibility and combined predictive value of potential biomarkers. Preferably, HD-related changes should be detectable over short intervals in order to minimise the time needed for subsequent therapeutic trials to show an effect. Extended follow-up periods would seem useful to improve insight into HD clinical evolution.

Ideally, new promising biomarkers should be tested in large multicentre trials to increase sample size and uniformity in basic measures. The in 2007 started international TRACK-HD study was initiated to determine which measure or combination of measures is the most sensitive for detecting change in the natural course of premanifest and early HD, and to validate these as potential outcome measures for use in future therapeutic trials.[10] The present study shows that in addition to volumetric MRI, the quantification of hypointensities in the basal ganglia may reflect a specific neuropathological feature of HD, iron accumulation, and deserves further research. Also, EEG during cognitive challenging and ERP studies should be further investigated to show functional abnormalities when 'probing the weak spot'. Comparison to other neurodegenerative disorders would give more insight into the specificity of the measures studied.

The present findings demonstrate that small explorative studies are valuable. Core assessment protocols should then be used to improve comparability between studies. Currently, protocols for clinical and imaging data are developed in the EHDN.[16] A more standardised clinical assessment will also contribute to better criteria for the definition of premanifest HD and thus reduced variance in inclusion criteria for research purposes. A stringent cut-off of the UHDRS total motor score might improve the assumption that individuals are premanifest. However, 'forced' motor-based boundaries between groups inevitable create bias. The predictive value of markers should, therefore, also be tested in the continuum of premanifest to early manifest disease without pre-determined subgroups. Natural subgroups of phenotypical variation may emerge if no boundaries are established. Studies on early brain changes in HD should also focus on gene carriers who are still far from onset, to shed more light on the possibility that (functional) brain abnormalities may already be present decades before manifest disease and may give an indication of developmental pathology. It is preferable to select individuals close to onset for therapeutic trials.

This study shows that several biomarkers provide new and important information on premanifest HD. The multifactorial approach offers new insights into the relation between clinical phenomena and abnormalities in the neural substrate. The goal of future research into premanifest HD is to combine the currently acquired pieces of knowledge and to bridge the gap between clinical phenomena and changes in brain morphology and functioning.

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