

Progress in Huntington's disease: the search for markers of disease onset and progression

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Abstract:

Unlike most neurodegenerative disorders, individuals at risk from Huntington's disease can be identified prior to the onset of clinical signs of the disease by virtue of it being an autosomal dominant condition. This provides the hypothetical opportunity to delay disease onset and/or slow down the progression of the disease in the very early stages ahead of overt features of disease. To help prepare for therapeutic trials of disease modifying compounds extensive work has gone into: (1) finding ways of better predicting the onset of disease in pre-manifest HD gene carriers (PMGC), (2) defining the extent of non-motor features of HD and, (3) identifying robust and reliable tests by which to measure disease progression. In this short review we summarise some of the major findings in this area of clinical research.

Introduction:

Huntington's disease (HD) is an inherited progressive neurodegenerative disorder, characterised genetically by an unstable CAG expansion in exon 1 of the huntingtin gene and clinically by a triad of motor, cognitive and psychiatric deficits. Unlike many neurodegenerative disorders, the genetic origin of HD means that the disease can be studied even before a clinical diagnosis has been made. At present, gene carriers are diagnosed with manifest disease upon the emergence of overt motor signs of disease however, research has shown that cognitive abnormalities (Stout et al., 2011) and brain atrophy (Aylward et al., 1996) are both detectable many years prior to this point.

Over the last 10 years great investment has gone into better understanding this prodromal stage of HD with the aim of (1) find ways of better predicting when pre-manifest HD gene carriers (PMGC) will receive a clinical diagnosis, (2) to define the true extent of non-motor features of HD and, (3) to identify robust and reliable tests by which to measure disease progression. The field has been dominated by three large, multi-centre cohort studies: PREDICT-HD (Paulsen et al., 2008), the European Huntington's Disease Network's Registry study (Orth et al., 2010) and most recently TRACK-HD (Tabrizi et al., 2012, Tabrizi et al., 2011, Tabrizi et al., 2013a). All have taken a multimodal approach, using a combination of clinical measures, imaging and wet biomarkers, to interrogate the period immediately prior to and post clinical diagnosis in HD.

Data from the TRACK-HD study (Tabrizi et al., 2012, Tabrizi et al., 2011, Tabrizi et al., 2013b) suggests that baseline apathy scores, the ability to recognise negative

emotions and longitudinal changes in whole brain, grey-matter, white-matter and caudate volumes are all predictive of clinical diagnosis within a 3 year period in pre-manifest HD gene carriers. Conversely however, PREDICT-HD (Paulsen et al., 2008) found that it was subtle increases on the UHDRS total motor score, changes in putamen volume or a reduction on the Stroop word reading score that were the best predictors of clinical diagnosis over a 5 year period. This lack of consistency is further replicated in the wider literature across many studies (for a review see (Dumas et al., 2013a)). Therefore, even when a similar methodology is used in a similar group of participants there still appears to be a fundamental heterogeneity within the pre-manifest population that results in a lack of consensus about the measures which are the best predictors of clinical diagnosis.

Although, it is worth noting that the point of clinical diagnosis is a subjective and somewhat arbitrary milestone especially in reference to both the neuropathology and neurobiology of HD. This may therefore, contribute to the variability seen between and within studies striving to find predictors of “disease onset”. In which case, going forward a more scientifically appropriate approach may be to treat disease progression as a continuous variable, beginning almost from birth.

In this review we aim to summarise all the work on HD that has been published in the *Journal of Neurology* since 2012. Given that the aims discussed above, the studies concerned with predicting clinical diagnosis will be discussed first, followed by those which are applied across the disease spectrum and may therefore be useful for mapping disease progression.

1. Predicting clinical diagnosis in HD:

Neuropathology

Atrophy of the striatum has been reliably shown to occur a decade or more prior to the onset of motor features (Tabrizi et al., 2011, van den Bogaard et al.). There is also evidence of atrophy in many other brain structures including the frontal lobes, thalamus, globus pallidus and insula (Harris et al., 1999, Thieben et al., 2002, Paulsen et al., 2006, Aylward et al., 1998) with abnormalities in both white matter (Rosas et al., 2006, Dumas et al., 2012) and cortical grey matter (Tabrizi et al., 2011) during the pre-manifest stage. However there is still discussion about the relationship these abnormalities have with the onset of disease and whether they could also have some developmental basis. A cross-sectional analysis of the imaging data collected as part of the TRACK-HD study has shown that the nucleus accumbens, the caudate nucleus, the pallidum and the putamen all display a progressive reduction in volume which is disproportionate to whole-brain atrophy and is apparent from very early pre-manifest stages (van den Bogaard et al., 2011). In contrast, other structures such as the hippocampus, remain relatively preserved until almost immediately prior to disease onset but then decline rapidly in manifest disease. In addition, the loss of volume in the accumbens nucleus, putamen, pallidum and hippocampus was found to impact significantly upon clinical measures such as the UHDRS total motor score and total functional capacity suggesting a direct relationship between degree of atrophy and clinical outcome, which may therefore make them useful as very early markers of disease progression.

In this regard, Herben-Dekker and colleagues have demonstrated that glucose metabolism in the putamen, as measured by 18-fluorodesoxyglucose (FDG)-PET, was lower in a group of pre-manifest HD gene carrier compared to controls (Herben-Dekker et al., 2014). In this study, participants were grouped according to their proximity to disease onset, based upon the outcome of a neurological examination 10 years after their baseline scan. Those participants identified as being “close” to onset (e.g. within 10 years of a diagnosis) all had low-average or abnormal putaminal metabolism at a 2 year follow-up scan whereas the far group all had normal metabolism in this structure.

This data would appear to suggest that the putamen may be a promising biomarker by which to identify PMCG’s at immediate risk of receiving a clinical diagnosis although, before this can be fully established longitudinal analysis of changes in the putamen is needed in a larger cohort of patients.

Lifestyle factors

The age at which at risk individuals present with overt signs of HD is hugely variable. While CAG repeat length can account for between 50%-69% of this variance, the other factors behind this variability remain unexplained. Other genetic factors are likely to contribute to this relationship as are environmental influences. Researchers from the University of Iowa studied the role of substance abuse on age of onset in 136 HD patients who presented at the University of Iowa Huntington’s disease Society of America (HDSA) Centre of Excellence outpatients clinic between 1997 and 2009 (Byars et al., 2012). They collected information on current and previous drug, alcohol

and tobacco abuse by participants and accompanying family members as part of the Unified Huntington's Disease Rating Scale (UHDRS) assessment. Where possible this information was verified using the patient's medical records. Participants with a history of drug or alcohol abuse were found to have a significantly earlier age of onset compared to those who did not. A similar trend was observed for tobacco abuse although this failed to reach significance. This effect was predominantly seen in women where the presence of at least one substance abuse factor, regardless of type, was associated with a significantly younger age of onset. Of course it is not clear whether this "abuse" brings out the disease or is an early feature of the condition.

However, the authors do acknowledge several shortcomings of this study including the retrospective data collection and the lack of a formal diagnosis of "abuse"; relying instead upon the opinion of the participant and/or family member. In addition, information about the duration or extent of abuse was not available to the study team. Therefore, it is difficult to evaluate whether these findings are reflective of abuse or just periods of increased and/or excessive use. Without this additional information the data from this study cannot be used to predict patients who are at increased risk of phenocopying early as it is not possible to establish whether there is a linear relationship between these two factors (i.e. as the extent of abuse increases the age of onset decreases) or if it is truly categorical as suggested in this article (i.e. abuse equals earlier onset, no abuse equals later onset).

Other studies have reported that environmental factors such as increased caffeine intake (Simonin et al., 2013) and more time spent in education (Lopez-Sendon et al., 2011) are also associated with an earlier age of onset. Despite this, the question

whether early behaviour can impact upon the profile of disease experienced in later life is an interesting one and warrants further investigation.

2. Mapping disease progression:

Cognition

Executive processes are profoundly affected as a result of the disease process in HD, with deficits resembling those seen in patients with lesions to the frontal lobes. This pattern of impairment is believed to be a direct result of loss of functional integrity in the frontostriatal networks. Abnormalities in manifest disease has been found on a range of different tasks including measures of attention (Lawrence et al., 1998), planning (Watkins et al., 2000, Papp et al., 2013) cognitive inflexibility (Lawrence et al., 1999) and working memory (Pirogovsky et al., 2009, Stout et al., 2011, Dumas et al., 2013b). Hart and colleagues (Hart et al., 2012) looked at electrical brain activity in relation to high-order cognitive functioning in HD using a measure of attention control in combination with EEG. Abnormalities in event-related brain potentials (ERP's) were found in mild HD, but not pre-manifest gene carriers, on a simple sustained attention to response test (SART). Specifically, patients with mild HD made more Go-errors (failing to respond to stimuli that they should respond to) when compared to both pre-manifest HD and controls with most Go-errors being made directly following a no-Go error. Contrary to previous literature, there was no difference between groups on no-Go error rates. Response times for trials immediately surrounding an error were suggestive of a deficit in attention control in participants with mild HD with a drop in reaction time (RT) immediately prior to the error. HD patients also found it difficult to recover from their errors, taking several trials to return to pre-error levels of responding, although this may equally reflect a

difficulty in switching between Go and no-GO trials. Longer P300 latencies, indicating a lower speed of attentional processing, on both Go and no-Go trials is supportive of a disturbance in attentional control in patients with mild HD. Furthermore, a second, pilot study from the same research group identified an increase RT longitudinally over 3 years in manifest patients with greater effects seen in trials preceding a correct no-Go trial which was replicated in pre-manifest HD in the absence of any cross-sectional differences (Hart et al., 2013). The relative simplicity of this task makes it an ideal candidate as an outcome measure for future trials of cognitive enhancing compounds in HD.

Learning and memory deficits have been found in both early and pre-manifest HD with abnormalities detected more than a decade from disease onset (Solomon et al., 2007). However, the neuropathological origin of these early cognitive changes is currently poorly understood. While the characteristic loss of striatal integrity seen in HD is believed to play a role, the hippocampus is known to be a key brain region involved in the formation of new memories (Scoville and Milner, 1957). Elevated cortisol levels have been associated with both poorer learning and memory performance (Csernansky et al., 2006) and damage to the hippocampus (Sapolsky, 2000) and while it has been reported in many neurodegenerative and neuropsychiatric disorders it has never been formally assessed in HD.

Shirbin and colleagues however, looked at the relationship between elevated cortisol levels and learning and memory in HD (Shirbin et al., 2012). The release of cortisol in response to psychological and physical stressors is mediated by activity in the hypothalamic-pituitary-adrenal (HPA) axis; this neuroendocrinological system has

been shown to be abnormal in HD and may have value as a possible biomarker of disease progression (Petersen and Bjorkqvist, 2006).

In this study, higher evening cortisol levels were associated with a worsening impairment in learning and memory performance assessed by the California Verbal Learning Task – second version (CVLT-II) in patients with early HD, and those with a higher UHDRS total motor score. It was noted that the relationship was more robust when the UHDRS was used as a continuous variable compared to the group based analysis (pre-HD Vs early-HD). No relationship was found between recognition memory and cortisol levels. The authors interpret their results as evidence of a link between dysregulation of cortisol concentration levels and decline in learning and memory performance in HD.

The results of this study are principally descriptive and not able to identify causality. While they imply a relationship between levels of cortisol concentration and cognitive performance it is unclear whether this is mediated by other factors such as disturbances in the sleep-wake cycle which has also been shown to be affected in HD (Goodman et al., 2011). Furthermore, the sample size was small, especially when the cohort was dichotomised based upon clinical diagnosis (pre-HD Vs early-HD), which ultimately reduces the statistical power of the study to detect a relationship.

One of the challenges in mapping the natural history of the cognition changes experienced by HD patients is that there are few neuropsychological tasks that are relevant at all stages of the disease. Most will result in either ceiling effects when used with pre-manifest participants or floor effects when testing advanced patients. Begeti

et al (Begeti et al., 2013) assessed performance on the Addenbrooke's Cognitive Exam-Revised (ACE-R) as measure of global cognitive performance in a large cohort of HD participants ranging from pre-manifest gene carriers to patients with advanced disease. The ACE-R was chosen because it is freely available, relatively quick and easy to administer without the need for dedicated training. In addition it encompasses the Mini Mental State Exam (MMSE) which has been used traditionally to measure global cognition but contains additional subsections, particularly in the domain of executive function, making it more sensitive in HD.

It was shown that the pattern of impairment identified by the ACE-R changed as the disease progressed. In the pre-manifest stage, impairments were found to be selective with deficits on phonemic, but not semantic fluency only, although performance did not correlate with estimated time to disease onset. By early disease however, patients demonstrated deficits on the majority of subdomains with preservation of only the attention and language sections. Despite this, a distinct pattern of impairment can be seen in both moderate and advanced disease making the ACE-R a practical and meaningful way of assessing cognition across the entire disease course. However, it should be noted that while this study included follow-up data for a small sub-population of patients, over a relatively short period, further work is needed to establish whether these cross-sectional findings can be replicated through longitudinal follow-up of large cohorts of patients.

Automatic Nervous System

Although often under reported, dysfunction of the autonomic nervous system (ANS) can be a feature of HD, presenting clinically as gastrointestinal, urinary, cardiovascular and sexual problems (Aziz et al., 2010). While there is evidence of subtle ANS dysfunction in the pre-manifest stage of disease (Aziz et al., 2010, Kobal et al., 2010, Andrich et al., 2002) the neuropathological basis of these abnormalities is unclear.

Melik and colleagues (Melik et al., 2012) used a novel task which was believed to be sensitive to very subtle differences in ANS function. The microcirculatory response to local cooling as a sensor stressor in pre-manifest and early stage HD participants was examined along with cardiovascular autonomic testing.

In general, the HD groups as a whole had a higher blood pressure and heart rate than controls, however, their response to cooling was less pronounced. The normal physiological response to an acute stressor such as local cooling is decreased skin blood flow, increased blood pressure and a fall in heart rate (Johnson and Kellogg, 2010, Minson, 2010). In this study, pre-manifest HD participants exhibited an exaggerated microcirculatory response to cooling compared to controls.

The profile of heart rate variability differed between the two HD groups with manifest HD participants exhibiting lower low frequency and greater high frequency variability than both the pre-manifest group and controls. One possible explanation for this is that the variability in heart rate occurs as a result of differences in the emotional state of the participants. For example, it may reflect a lower level of anxiety in response to

the stressor in the manifest HD patients compared to the other groups although unfortunately this was not assessed during the study.

In a further study the sensory stressor was replaced by a cognitive stressor (mental arithmetic) (Kobal et al., 2014). In this scenario the microcirculatory response to the stressor was equivalent between the pre-manifest group and controls, however the magnitude of the effect seen in manifest patients was attenuated. Relative laser Doppler flux (laser Doppler flux during mental arithmetic expressed as a percentage of laser Doppler flux resting rates) increased with advancing motor disease suggesting that the cognitive stressors produced less of a cutaneous microvascular response as the disease progresses. Furthermore, the heart rate of both HD groups increased less than controls during the mental arithmetic task while the increase in blood pressure was equivalent between all three groups.

Together, these studies suggest that there are problems in the ANS in HD although, how these abnormalities evolve across the duration of the disease and how they relate to central HD pathology is still somewhat unclear. Therefore, further work is needed to clarify the situation.

Quality of life

As disease advances patients with HD often struggle to complete self-report assessments due to both physical difficulties and a lack of insight into their problems.

In those situations the opinion of a proxy is often sought to provide information on subjective measures such as the patient's thoughts, beliefs and quality of life.

Researchers from the University of Reading compared the responses given by 105

people living with HD to the scores given by their proxy on an HD specific measure of health related quality of life to assess inter-rater reliability (Hocaoglu et al., 2012). Typically there was good patient-proxy agreement especially for those patients in the early and late stages of the disease with less patient-proxy agreement seen when the patients were in the middle stages of the disease. When there was patient-proxy disagreement the more subjective subscales such as the Specific Hopes and Worries Subscale were generally scored more optimistically by proxy's than by patients; the reverse of which is true for both the Specific Cognitive and Specific Physical and Functional Scales. It was noted however, that proxies' ratings of psychosocial aspects of quality of life such as on the Specific Hopes and Worries, Specific Mood State and Specific Self and Vitality scales, is influenced by the patients psychological state. This study provides evidence that the proxy version of the HDQoL is a useful scale that can be used both in combination with, or as an alternative to the self-report version.

Conclusions

The broad scope of the research reviewed here demonstrates the range of different approaches that are being taken to prepare for future therapeutic trials in HD; not just those which are targeted at delaying the onset and/or slowing down the progression of the disease but also extensive work into measure that can also be used in manifest disease. To assist with this, extensive work has gone into better defining the clinical phenotype of HD, to creating new assessment tools to capture the complexity of the symptoms experienced by patients suffering from HD and to better understand factors which influence and mark the onset and progression of the disease. Hopefully, this work will soon be used to take novel therapies from the lab into the clinic.

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Conflict of interest

The authors have no conflict of interest to report.

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