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“Pre-symptomatic” Huntington's disease

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55.1. Introduction

Publication of the human genome has accelerated the paradigm shift in medicine from treatment of disease following diagnosis to the prediction and prevention of disease in healthy persons. Huntington's disease (HD), an autosomal dominant progressive neurological disease with an identified gene mutation (Huntington's Disease Collaborative Research Group, 1993), could prove to be a useful model in preparing for preventive clinical trials in other neurodegenerative diseases because individuals with the gene expansion can be identified years before diagnosis through genetic testing. This chapter will review current diagnostic procedures for HD, with a focus on recent developments in the identification of the earliest signs and symptoms of pre-diagnosed individuals carrying the gene expansion for HD. Additionally, we will highlight some clinical information that could be used to select these individuals in preparation for preventive clinical trials.

55.2. Huntington's disease at diagnosis

HD is a neurodegenerative disorder affecting the basal ganglia and associated circuitry, with loss of medium GABAergic spiny neurons, sparing of the large cholinergic interneurons (Ferrante et al., 1985; Calabresi et al., 1998), and specific neuronal loss in layers V and VI of cerebral cortex (Hedreen et al., 1991). Morphometric analyses have suggested early thinning of the cortical ribbon (Rosas et al., 2002), as well as volume reductions in almost all brain structures, including the caudate, putamen, globus pallidus, amygdala, hippocampus, brainstem, and cerebellum (Jernigan et al., 1991; Rosas et al., 2003). These physiological changes lead to an insidious decline in motor, cognitive, and psychiatric functioning, a diminished quality of life, and premature death for individuals carrying the mutated polyglutamine repeat sequence (Nehl and Paulsen, 2004). Currently, the accepted practice parameters for diagnosing HD require the onset of voluntary and involuntary motor abnormalities in a person at risk by family history. For example, the presence of chorea, motor impersistence, and/or impairments of saccades, along with a family history, are likely to be sufficient evidence for diagnosis. Nonetheless, cognitive deficits (Hamilton et al., 1999; Rohrer et al., 1999; Paulsen et al., 2001a; Sadek et al., 2004) and psychiatric symptoms (Litvan et al., 1998; Paulsen et al., 2001b, 2005; Hamilton et al., 2003; Beglinger et al., 2007) are also frequent manifestations of the condition, but have traditionally not been viewed as diagnostic signs. Similarly, structural imaging changes, especially those involving

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the striatum (i.e., caudate and putamen), have been widely reported as the gross neuropathological markers of HD, but these occur relatively late, have not been used for clinical diagnosis and tend to only serve as supportive evidence. It has been reported that loss of caudate volume exceeds 50% by the time of diagnosis (Aylward et al., 1997, 1998, 2000); similar gross atrophy is evident on neuropathological examination as well (Vonsattel et al., 1985).

Recent research, however, suggests that subtle signs and symptoms of HD may be present years or even decades before diagnosis in individuals who are healthy but carrying the mutated gene. A few small studies have identified differences between pre-diagnosed, gene-expanded individuals and controls on neuroimaging (Paulsen et al., 2004, 2006b), cognition (Nehl et al., 2001; Paulsen et al., 2001a), and psychiatric symptomatology (Nehl et al., 2001). These studies support the need to investigate HD at its earliest point. This type of investigation is all the more critical considering that there is currently no cure for HD. Several clinical trials are investigating means to alleviate or reduce symptoms and slow its progression. Consistent with other medical conditions, preventive treatments might be ideally initiated at or before the earliest signs of disease. Therefore, we will review one recent attempt to identify pre-diagnosed HD by tracking individuals who have the gene expansion but are currently healthy.

55.3. Huntington's disease before diagnosis: the Predict-HD study

Neurobiological Predictors of Huntington's Disease ("predict-HD"; NS40058, PI JS Paulsen) is a multi-site, longitudinal, observational study aimed at identifying biological and refined clinical markers of early HD in humans and then validating the optimal marker(s) and clinical endpoints for use in preventive clinical trials. Participants from the USA, Canada, Europe, and Australia undergo annual study visits consisting of a neurological motor examination, cognitive assessment, brain MRI, psychiatric and functional assessment, and blood draws for genetic and biochemical analyses. Predict-HD has enrolled more than 850 gene-expanded but not diagnosed participants, as well as a smaller sample of demographically matched non-gene-expanded participants ($n \approx 85$) who serve as a comparison group. Results of initial analyses of the data have been reported elsewhere (Paulsen et al., 2006a; Paulsen et al., in preparation), but will be summarized below.

The primary clinical outcome for Predict-HD is phenoconversion from pre-symptomatic to diagnosed HD. Since the purpose of the study was to investigate the earliest signs and symptoms of HD, most of the participants were purposely selected to be "far from onset" (i.e., genetically and motorically distant from diagnosed HD), and few participants have been diagnosed with HD at this point. Therefore, a proxy measure of "estimated years to HD diagnosis" was developed using DNA and current age. This measure was based on a survival analysis regression equation using CAG repeat length and a retrospectively determined age at motor diagnosis (Langbehn et al., 2004).

55.3.1. Motor signs

Results from a neurological examination indicated that the majority of gene-expanded participants were rated as having no motor signs (33%) or minor motor signs (44%),

although 15% were considered to have “possible HD” and 5% of individuals were rated as “probable HD”. For these gene-expanded individuals, motor scores were strongly, but non-linearly, related to estimated years to HD diagnosis. This curvilinear trend (see Fig. 55.1) indicates relative stability in motor scores until 10–15 years before diagnosis, at which point motor functioning begins to deteriorate more rapidly. Among the pre-diagnosed participants, certain motor abnormalities were more often abnormal compared to controls, and these included chorea, bradykinesia (especially finger tapping), and oculomotor impairments (see Fig. 55.2). Interestingly, some of the non-gene-expanded participants also were rated as demonstrating motor signs of HD (32% minor signs, 6% possible HD), although the vast majority (62%) were deemed free of motor signs. Although the motor exam maybe the most widely used method of assessing motor signs in HD, supplementary methods have been explored in this sample (e.g., video motion analysis; Delval et al., 2006; quantitative oculometry; Ali et al., 2006).

55.3.2. Neuroimaging

Prior research has indicated that the striatum is one of the primary areas of neuropathological degeneration in HD, so this became an initial focus of neuroimaging in the Predict-HD study. For gene-expanded individuals, the volume of the striatum was strongly related to motor functioning, with the greatest volumes occurring in individuals with no motor signs (mean striatal volume $\frac{1}{4}$ 17.06) and the smallest volumes in those with “probable HD” (mean striatal volume $\frac{1}{4}$ 14.89). As these participants got closer to their estimated age of diagnosis, the size of the striatum begins to decrease, again in a curvilinear pattern like the motor scores (see Fig. 55.1). This pattern is consistent with previous findings (Aylward et al., 1994, 1997, 2000, 2004). While much less focus has been placed on regions outside the striatum, structural imaging studies in patients diagnosed with HD suggest that the pathology of HD is widespread. All such studies have found a low volume of cerebral white matter in patients with HD (Jernigan et al., 1991; Aylward et al., 1996, 1998; Rosas et al., 2003; Fennema-Notestine et al., 2004). In the only quantitative MRI study to date on presymptomatic HD subjects, our group found that 24 pre-symptomatic subjects had significantly larger volumes of cerebral cortex while the cerebral white matter was decreased in volume compared to controls (Paulsen et al., 2006b). Only after significant degeneration would this enlarged cortex become lower than normal, thereby giving the appearance that it was “spared” (see Fig. 55.3). These and other structural imaging techniques (e.g., tensor-based morphometry; Kipps et al., 2005) hold promise as endpoints in preventive clinical trials of HD.

Additionally, functional neuroimaging is a useful tool to assess for changes that may predate structural degeneration. We recently found cerebral blood flow alterations during a spatial working memory task in pre-symptomatic participants compared to healthy controls who completed O15-labeled water positron emission tomography (PET). Specifically, the participants who were gene-positive for the HD trinucleotide expansion showed decreased activation in the caudate compared to controls (see Fig. 55.4). Using functional MRI (fMRI), similar results were obtained in 14 participants with pre-symptomatic HD who were divided into “far from onset” and “close to onset” groups. Pre-symptomatic participants who were “far from onset” (i.e., greater than 12 years from estimated onset) showed hyperactivation of

medial prefrontal regions (see Fig. 55.5). Feigin et al. (2006) also demonstrated increased activation of the precuneus compared to controls on a motor sequencing learning task in presymptomatic HD. These examples of abnormally increased activation might reflect a compensatory mechanism; that is, increased function to compensate for structure abnormalities. Ultimately, functional neuroimaging has been used to identify abnormal brain processes many years from estimated disease onset.

55.3.3. Cognitive

The cognitive assessment component of Predict-HD consists of both clinical and experimental cognitive tests that were selected to be sensitive to basal ganglia dysfunction and/or HD, based on animal and human studies. These tests are administered in both paper-and-pencil and computerized format, and tap six cognitive domains, including psychomotor speed, timing and movement sequencing, learning and memory, working memory, face and emotion recognition, and executive functions. Across cognitive domains, worse motor functioning was associated with poorer cognitive performances for gene-expanded individuals (Paulsen et al., 2006a; Solomon et al., 2007). Several cognitive measures displayed significant curvilinear trends with estimated years from HD diagnosis. For example, the speeded finger-tapping task was relatively stable until 10 years from estimated disease onset, at which point it declines precipitously (see Fig. 55.1). Performances on two other cognitive tasks, self-paced finger-tapping and word-list learning, show similar curves, although the point of declining performance is further from estimated onset. Additionally, the relationship between cognition and estimated years to disease diagnosis remains even after controlling for motor scores. It should be noted, however, that most cognitive scores did not fall in the impaired range when compared to normative data—these are subtle declines. Recently, Solomon et al. (2006) found dissociation between an explicit memory task correlating with caudate volume and an implicit memory task with a motor component correlating with putamen volume, but not vice versa. This suggests that, even in a sample of pre-symptomatic participants, there is functional segregation of the striatum. Such findings implicate the basal ganglia in both motor and cognitive functions and raise the question of whether a simple motor definition for the diagnosis of HD might be limited. Although HD can lead to dementia in later stages, pre-diagnosis and early diagnosed stages of the disease clearly demonstrate subtle cognitive changes, and these findings are consistent with several other lines of research (Boulet et al., 2005; Brandt et al., 2005; Yaguez et al., 2006).

55.3.4. Psychiatric

Some have suggested that psychiatric manifestations may be the earliest signs of HD (Brandt et al., 1989; Berrios et al., 2002; Kirkwood et al., 2002), and Predict-HD has sought to capture this potentially important information by sampling a range of behavioral disturbances, including depression, hopelessness, and emotional distress. Using self-report and companion-rated measures, the average level of distress of the participants with the HD gene expansion was greater than that in the comparison group without the HD gene expansion (Paulsen et al., 2006a; Duff et al., 2007). Additionally, levels of distress were positively associated with motor scores, so that participants with no motor signs tended to be psychologically healthier than those with “probable HD” (Duff et al., 2007). Like the cognitive scores, the average scores across the gene-expanded group did not exceed clinical

cutoffs for all psychiatric measures, indicating relatively mild symptomatology. As patients approach diagnosis, impairments in insight could interfere with accurate report of psychiatric symptoms (Ho et al., 2006), so companion reports and other objective measures of psychophysiological functioning might be better indicators of psychiatric distress.

55.3.5. Summary

Results from preliminary analyses of Predict-HD provide multimodal convergence of curvilinear trends across motor functioning, striatal volume, and cognitive performances. These initial findings are encouraging in the search for markers of disease progression and endpoints to use in preventive clinical trials. Future analyses of this ongoing study will examine the independence of these potential markers to find which variable or combination of variables best predicts HD diagnosis. This study will also serve as a launching pad for future preventive clinical trials, in terms of recruitment, methodology, and infrastructure. Finally, it is hoped that Predict-HD and similar studies will serve as a model for the study of other neurological and psychiatric diseases.

55.4. “Diagnosing” pre-symptomatic Huntington’s disease

In light of the preliminary findings of Predict-HD, several important issues are raised regarding the “diagnosis” of pre-symptomatic HD. We use the term “diagnosis” broadly, which could imply that formal clinical criteria have been met. Currently, however, no formal diagnostic parameters exist to diagnosis HD. Criteria do exist to define dementia in this neurological condition (American Psychiatric Association, 1994), but they lack any specificity for HD. Despite clear cognitive impairments in so-called “at-risk” HD participants, less than 1% of our sample met DSM criteria for dementia although functional changes had occurred. Additionally, the formal diagnosis of pre-symptomatic HD remains a controversial issue with important ethical, social, legal, and medical implications. Taken another way, “diagnosis” could also imply the identification of a condition by its signs and symptoms. Using this latter view of “diagnosis”, Predict-HD sought to identify biological and clinical markers of early HD that might be used as clinical endpoints in preventive medication trials. This study also sought to identify appropriate samples for those clinical trials. The identification of individuals at greater risk of converting to HD is appealing from a research perspective because it could lead to more efficient clinical trials by using enriched samples (i.e., persons with a high likelihood of phenoconversion). From a clinical standpoint, the early identification of disease onset could also have advantages, such as advanced planning for medical and legal decision-making, initiating treatment plans, and making lifestyle choices (e.g., work, living arrangements). However, early diagnosis must also be weighed with its potential risks, which might include increased stress, changes in social relationships, and discrimination (e.g., loss of insurance coverage). Penziner et al. (2005) examined perceptions of genetic discrimination in participants with the HD gene expansion and found that although the majority of employed participants (78%) had revealed their genetic test results to their current employers, nearly all of them reported that they would not disclose this information to future employers.

We are not necessarily advocating for the diagnosis of pre-symptomatic HD, but further clarification of this phase of the disease is needed. We are, however, clearly advocating for

more sophisticated clinical care and research endeavors in HD. Below is a list of some recommendations for individuals who are also pursuing this goal.

55.4.1. Clinical and research considerations

55.4.1.1. Gene testing—“Diagnosis” of HD should include a gene test. Testing for CAG repeat length is an important part of clinical care, whether the diagnosis is meant to determine symptomatic status (i.e., supporting a diagnosis) or presymptomatic status (i.e., confirming risk status). Since there are multiple neurological conditions that can present with motor abnormalities that might suggest HD, only the expanded gene sequence can provide the clinical confidence necessary to diagnose. As part of the inclusion criteria, Predict-HD used a CAG repeat length in the HD range (i.e., greater than or equal to 39) because shorter repeat lengths (i.e., 30–38) tend to be less reliable.

55.4.1.2. Aggregate clinical data: All available clinical data provide support, for or against, the diagnosis of HD. Whereas the presence of motor signs is typically crucial for this diagnosis, 20% of the Predict-HD gene-expanded but not diagnosed sample showed motor signs consistent with “possible” or “probable” HD, as determined by trained motor raters. Additionally, 6% of non-gene-expanded controls were rated as having “possible” HD based on a motor exam alone. Other clinical data, such as imaging, cognitive, and psychiatric profiles, can contribute to the diagnosis of HD. Striatal volume, for example, significantly decreased as individuals approached diagnosis. Similarly, performances on a range of cognitive tasks declined for individuals who were approaching diagnosis, even after controlling for motor functioning. Lastly, psychiatric ratings, both by participants and their companions, worsened as they got closer to diagnosable HD. These preliminary results from Predict-HD are cross-sectional, so longitudinal data (which are currently being collected) will be needed to confirm these findings. Nonetheless, these results provide additional support for the inclusion of all available clinical data in cases of patients with suspected HD.

55.4.1.3. Predicting clinical onset: Both CAG repeat length and other clinical markers can provide information about clinical onset in presymptomatic individuals.

(a) Estimated years to diagnosis is calculated with current age and CAG repeat length, using the formula of Langbehn et al. (2004). This information could be useful for participant selection or measuring outcome. For example, if a drug is being used to delay conversion to HD, then individuals might be selected who are “close to onset” to maximize the number of potential converters across a given period. Additionally, this information could be used to compare estimated time to onset with actual time to onset to see whether a drug did indeed delay conversion to the disease.

(b) Given the convergence of curvilinear trends in motor, neuroimaging, and cognitive data for gene-expanded but not diagnosed individuals, it is likely that further refinement is possible of the existing, disease-onset prediction formulas (Langbehn et al., 2004), such as by combining them into a multimodal equation with minimal redundancy in accounted-for variance. Our initial analyses suggest that other clinical data can uniquely contribute to the prediction of estimated years to onset of HD, and will provide better estimates for a wider range of “at-risk” individuals. Similar types of regression-based prediction formulas have

already been used to assist in tracking cognition in epilepsy (Sawrie et al., 1996) and possible dementia (Duff et al., 2004). In these formulas for HD, baseline data (including demographic information, CAG repeat length, and baseline “score”) are used to predict a future “score”. Given the available data in Predict-HD, the “score” could be motor functioning, striatal volume, cognitive test performances, or psychiatric ratings. As with the estimated years to onset formula, estimated score is compared to actual score to see whether the participant's course is consistent with stability or a significant deviation from the expected pathway. The development and validation of these formulas require large numbers of participants, but Predict-HD will be able to provide the necessary data. It is also anticipated that phenoconversion to HD (i.e., disease onset) will no longer be the outcome measure of choice in preventive trials. Rather, success will initially be judged by an intervention's ability to delay the downward deflection of functioning.

(c) Although CAG repeat length and current age can provide more specific information about clinical onset of HD, other biologically based markers are also being considered as modifiers of the phenotype of HD (e.g., levels of mutant huntingtin; Graham et al., 2006). Additionally, it is likely that environmental, non-genetic factors influence disease onset. For example, Friedman et al. (2005) reported on a set of monozygotic twins (i.e., genetically identical, including the same CAG repeat) who developed HD 7 years apart. Georgiou et al. (1999) also reported differential presentation of signs and symptoms of HD in a pair of monozygotic twins.

55.4.1.4. Terminology: “Pre-symptomatic” seems to be a misnomer. Predict-HD has already corroborated a small body of research that has described early changes in healthy, non-diagnosed individuals with the gene expansion for HD. These changes—motoric, cognitive, psychiatric, and/or neuropathological—appear to occur about 10–15 years before disease onset, if not more. Previously, any individual who had not yet been diagnosed with HD would be identified as “presymptomatic”. Given our current state of knowledge, that term does not appear to apply. Although it is unclear whether “pre-clinical” or “pre-diagnosed” or “pre-motor” will become the new descriptor, these individuals have signs and symptoms of HD. Future investigations might determine just how far out these symptoms occur (e.g., congenital), which could lead to a shift in diagnostic practices.

55.4.1.5. HD misconceptions: HD myths need to be challenged. Overall, the results of Predict-HD have challenged some of the long-held myths of HD. For example, it has been thought that studies of this rare neurological disorder would suffer from small sample sizes, yet the current collaborative project has recruited over 850 participants. Previously, motor abnormality was considered the sine qua non of HD, but scores on a motor examination might not be the only—or even the best—method for diagnosing HD. Despite the importance of the striatum as a neuropathological marker of HD, extrastriatal abnormalities continue to spark interest (Rosas et al., 2002; Fennema-Notestine et al., 2004; Beglinger et al., 2005). One final myth that this study would like to draw attention to and challenge is that HD is not curable. Beverly Davidson and other investigators at the University of Iowa have recently used RNA interference to silence the gene expression in mouse models of HD and other spinocerebellar ataxias (Harper et al., 2005). In addition to challenging myths in

HD, Predict-HD can serve as a model for the investigation of other neuropsychiatric disorders.

In conclusion, although HD is a devastating illness, its genetic transmission allows a unique opportunity to study the disease before diagnosis. Studying a relatively pre-symptomatic disease is not unique in neurology (e.g., mild cognitive impairment; Petersen et al., 1999; vascular cognitive impairment; Bowler, 2005), but studying gene-expanded but otherwise healthy individuals does provide valuable information about the “true” natural history of the development of the disease. Predict-HD has already provided glimpses into the transition from a healthy state to a disease state, and can serve as a model for many other diseases with genetic components, both neurological and non-neurological.

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Fig. 55.1.

These plots demonstrate the relationship between various markers of disease progression and estimated years to diagnosis based on Langbehn et al. (2004). Motor exam score is based on the UHDRS, with higher scores indicating more motor dysfunction. Striatal volume is based on MRI. Speeded and self-timed finger-tapping are based on computerized cognitive testing, with higher scores indicating better functioning. Word-list learning is based on HVLT, with higher scores indicating better functioning.

Fig. 55.2.

Cases are presymptomatic individuals (i.e., CAG-expanded but not diagnosed with HD) and controls are “at-risk” individuals (i.e., non-CAG-expanded but with family history of HD). Total score based on all items of the UHDRS Motor Examination. Other items represent one or more individual items from the UHDRS Motor Examination.

Fig. 55.3.

*Different from controls, $P < 0.05$. Using MANCOVA, controlling for age, sex and total brain tissue volume. $N = 24$ controls, 12 “far from onset” (mean estimated years to onset $\pm$ 22 years), 12 “close to onset” (mean estimated years to onset $\pm$ 11 years), and 10 HD.

Fig. 55.4.

T-map showing reduced activation within caudate nucleus in Pre-HD (i.e., CAG-expanded but not diagnosed with HD) compared to controls (i.e., non-CAG-expanded but with family history of HD). Left panel, pre-HD; middle panel, control; right panel, randomization.

Fig. 55.5.

Volume activations for three brain regions for “at-risk” controls (i.e., non-CAG-expanded but with family history of HD), pre-symptomatic individuals who were “far from onset” (i.e., CAG-expanded, not diagnosed with HD, and an estimated time to onset of more than 15 years), and pre-symptomatic individuals who were “close to onset” (i.e., CAG-expanded, not diagnosed with HD, and an estimated time to onset of less than 15 years).