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Motor Abnormalities in Premanifest Persons with Huntington's Disease: The PREDICT-HD Study

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Abstract

Background—The PREDICT-HD study seeks to identify clinical and biological markers of Huntington's disease in premanifest individuals who have undergone predictive genetic testing.

Methods—We compared baseline motor data between gene-expansion carriers (cases) and non gene-expansion carriers (controls) using T-tests and Chi-Square. Cases were categorized as near, mid or far from diagnosis using a CAG-based formula. Striatal volumes were calculated using volumetric MRI measurements. Multiple linear regression associated total motor score, motor domains and individual motor items with estimated diagnosis and striatal volumes.

Results—Elevated total motor scores at baseline were associated with higher genetic probability of disease diagnosis in the near future (partial R2 0.14, $p<0.0001$) and smaller striatal volumes (partial R2 0.15, $p<0.0001$). Nearly all motor domain scores showed greater abnormality with increasing proximity to diagnosis, although bradykinesia and chorea were most highly associated with diagnostic immediacy. Among individual motor items, worse scores on finger tapping,

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tandem gait, Luria, saccade initiation, and chorea show unique association with diagnosis probability.

Conclusions—Even in this premanifest population subtle motor abnormalities were associated with a higher probability of disease diagnosis and smaller striatal volumes. Longitudinal assessment will help inform whether motor items will be useful measures in preventive clinical trials.

Keywords

Huntington's disease; at-risk; UHDRS

Introduction

Huntington's disease (HD) is typically an adult-onset, progressive and fatal neurodegenerative disease characterized by the clinical triad of a movement disorder, cognitive decline, and behavioral disturbances. It is autosomal dominant, caused by an expansion of a trinucleotide cytosine-adenine-guanine (CAG) in the 5′-translated region of the IT-15 gene on the short arm of chromosome 4.[1] The length of CAG expansion is inversely correlated with age at diagnosis.[1, 2] However, the precise point of disease diagnosis is poorly characterized, with clinical abnormalities emerging gradually over many years during a "premanifest" prodromal phase. [3, 7–10] Increasing evidence suggests that neuropathological changes may occur many years prior to the development of clinical changes.[4–6] Additionally, the degree of striatal atrophy correlates not only with disease severity in manifest patients[11], but also with estimated years to diagnosis in premanifest populations.[12–14]

The Neurobiological Predictors of Huntington's Disease (PREDICT-HD) study is designed to prospectively characterize refined clinical, neurobiological and neurobehavioral markers of Huntington's disease prior to the point of traditional clinical diagnosis in a population known to carry the HD CAG expansion[15]. Findings from the PREDICT study will identify critically important candidate outcome measures used in clinical trials aimed at delaying the diagnosis of illness. We have recently shown that most clinical indicators in the PREDICT cohort, including motor and neuroimaging markers, show subtle changes one to two decades prior to expected disease diagnosis.[16] The present analysis of the PREDICT cohort details the relationship of motor function, probability of disease diagnosis in the near future (based on CAG length and age) and striatal volumes.

Methods

Participant Eligibility

Participants were recruited from 30 sites in the United States, Canada, Australia and Europe. All participants were required to have voluntarily undergone genetic testing for the HD CAG expansion independent from the study. Institutional review boards at each participating site approved the study and each participant signed an informed consent. The Unified Huntington Disease Rating Scale (UHDRS) was used to determine whether each participant met criteria for a diagnosis of HD and only subjects considered premanifest by virtue of scoring a 3 or less on question 17 of the UHDRS (diagnostic confidence) were included in this paper. The diagnostic confidence question asks investigators to rate how confident they are that an individual at-risk for HD meets the definition of the unequivocal presence of an otherwise unexplained movement disorder on a scale from 0 (no abnormalities) to 4 (unequivocal signs of HD, ≥99% confident). Control subjects were

individuals who had tested negative for the HD CAG expansion, but were offspring of a parent with HD. Further details of the study have been previously reported.[15, 16]

Clinical Assessments

All participants underwent detailed motor, cognitive and psychiatric evaluations at baseline.[15] Neither participants nor raters were systematically blinded to gene status. The Motor section of the UHDRS was used to assess motor features at baseline and annually thereafter.[17] The motor UHDRS is a standardized assessment consisting of 31 items rated on a scale from 0 to 4 with a score of 0 indicating no abnormalities and 4 indicating severe impairment. The maximum possible total score is 124. Based on a factor analysis of the total UHDRS in patients with manifest HD, the motor items have previously been grouped into five factors; oculomotor, bradykinesia, rigidity, dystonia, and chorea.[18]

Probability of Diagnosis

Estimated years to diagnosis were calculated using a CAG and age based predictive model derived by Langbehn et al. and based on an analysis of 2913 individuals from 40 centers worldwide.[19] Consistent with previous reports involving the PREDICT cohort, cases were considered *far* from diagnosis if their estimated diagnosis was greater than 15 years, *mid* to diagnosis if their estimated diagnosis was 9–15 years, and *near* to diagnosis if their estimated diagnosis was less than 9 years. These definitions correspond roughly to tertiles of risk among our participants. The survival formula of Langbehn et al. can also be transformed to a probability of diagnosis within a given future time, based on a participant's CAG expansion length and current age.[16]

Magnetic Resonance Imaging

All scans for this project were obtained using a standard multi-mode protocol that included an axial 3D volumetric spoiled gradient echo series (~1×1×1.5 mm voxels) and a dual echo PDT2 (~1×1×3 mm voxels) series. All sites used a General Electric 1.5 Tesla scanner (with the exception of two sites: one using a 1.5 Tesla Siemens and one using a 1.5 Tesla Phillips scanner). Striatal volumes were expressed as percentage of total intracranial volume to control for variation in size.

To obtain measures of brain structure, first an approximate rough brain tissue region was obtained using the 3dskull from the AFNI tool suite[20]. Spatial intensity inhomogeneity correction fields were estimated over the brain tissue region and applied using tools described in Styner et al.[21] for each modality. An automated procedure rigidly aligned and resampled the 3 modes of each dataset into a $1mm^3$ isotropic voxel lattice where a line passing through the anterior commissure (AC) and posterior commissure (PC) is parallel to the horizontal voxel lattice, the inter-hemispheric fissure is aligned with vertical voxel lattice, and the AC point is located at the center of the voxel lattice.

Tissue classification[22] is performed using the BRAINS software suite[23]. Exemplars (2×2×2mm plugs) for grey matter, white matter and cerebrospinal fluid (CSF) are selected by randomly sampling the images and keeping those plugs with low variance under the assumption that they represent a single tissue type. The selected plugs are then assigned to a compartment using k-means clustering. The labeled plugs are then used to define discriminant functions. The discriminant functions are used to classify the multi-modal data, producing an image where each voxel location is labeled with a code representing the grey, white, and CSF composition. The intracranial volume (ICV) measure is composed of all tissue (grey and white matter) and CSF within the cranium, from just under the dura mater and below. Subcortical measures of the caudate, putamen, and thalamus are calculated using the automated neural network segmentation[24] tool from the BRAINS package.

The results of this procedure were visually inspected to verify that each stage was completed successfully. Greater than 90% of the scans analyzed passed all stages successfully. Scan failure was not significantly predicted by any of the variables (i.e., HD gene-expansion status or motor severity) that are the subject of this report.

Statistical Analyses—Comparisons between cases and controls were performed using T-tests and Chi-Square. All analyses were adjusted for age and gender. Linear regression models assessed the relationship between either total motor scores, motor domain scores or individual motor items and estimated diagnosis probability or striatal volume. We used diagnosis probability within 5 years rather than estimated years to diagnosis because diagnosis probability has consistently demonstrated approximately linear relationships whereas relationships involving estimated years to diagnosis are generally non-linear and require more complicated statistical models[16]. To control for starting morphological variability, we used the ratio of striatal volume (caudate plus putamen) to total intracranial volume in analyses involving those measures. Age and gender-adjusted associations with individual motor score components were calculated as partial R^2 statistics, derived from the corresponding regression models. We constructed multivariate regression models of the most important motor exam predictors of both diagnosis probability and striatal volume by using backwards selection techniques. Finally, Mantel-Haenszel Chi Square tests were used to assess monotonic trends between motor scores and proximity-to-diagnosis classification groups (far, mid, near). When relevant data were missing, participants were excluded from the analysis (7% of observations). An alpha level of 5% was used for significance testing.

Results

Baseline Characteristics

From October 2002 until October 2007, 929 participants were enrolled and had relevant baseline data available. Of these participants, 733 (79%) were expansion positive (cases), and 196 (21%) were expansion negative (controls). The majority (82%) of the cases were deemed to be either normal or have non-specific motor signs (diagnostic confidence level 0 or 1), 12% had diagnostic confidence level 2, and 6% had diagnostic confidence level 3 on examination at baseline. An additional 30 cases were excluded from analysis because of uncertain specific CAG length information at the time of analysis. For the 733 cases, 277 (38%) were predicted far, 252 (37%) mid, and 184 (25%) being near to estimated age of diagnosis. At the time of data analysis, MRI data were available on 500 cases and 150 controls.

Table 1 summarizes the baseline demographics, motor scores, probability of disease diagnosis and striatal volumes of cases and controls. In addition, demographic data separated by estimated diagnosis categories are given. Cases were slightly younger, had an older age of parental disease diagnosis, had worse total motor scores and worse motor domain scores and smaller striatal volumes than controls ($p<0.0001$ for all). Worse total motor scores ($p<0.0001$), worse motor domain scores ($p\leq0.001$ for all domains, except rigidity) and greater striatal atrophy ($p<0.001$) were associated with closer proximity to age of diagnosis in cases. Younger parental age of diagnosis ($p=0.015$) and male gender ($p = .04$) were also associated with closer proximity to age of diagnosis. As a consequence of the group definitions, older age ($p<0.0001$) and longer CAG repeat length ($p<0.0001$) were associated with closer proximity to diagnosis. Mean estimated probability of disease diagnosis ranged from 5% in the far from diagnosis group to 20% in the mid to diagnosis group and 46% in the near to diagnosis group.

Figure 1 shows the box plots of total motor score for controls and cases by proximity to diagnosis categories (far, mid, near).

Motor Assessments and Probability of Diagnosis

Table 2 shows the multivariate regression of total motor scores on probability of disease diagnosis. Worse total motor score at baseline was associated with a greater probability of disease diagnosis ($p<0.0001$) and accounted for 14% of the variance in the probability of diagnosis.

When evaluating each motor domain individually, bradykinesia accounts for 14%, chorea for 6% and oculomotor for 7% of the variance in the probability of diagnosis (see Table 3). If, as an additional step, we simultaneously adjust for all motor domains, only worse scores on the bradykinesia and chorea domains are uniquely associated with a greater probability of diagnosis. Allowing these domains to compete in a backwards-selected reduced model, bradykinesia ($p< .0001$) and chorea ($p = .0005$) remain significantly associated with probability of diagnosis. Oculomotor signs were the third most important domain, but were not significant.

Table 4 shows the simultaneous multivariate regression of all motor items on probability of diagnosis. Bradykinesia and oculomotor domains are broken into their component motor items. In this analysis where all motor items are included, worse scores on finger tapping, tandem gait, Luria, saccade initiation, and chorea show unique positive association with a greater probability of diagnosis. Controlling for all other motor signs, ocular pursuit had some negative association ($p = .01$) with diagnosis probability. No changes were noted with backwards variable selection.

Motor Assessments and Striatal Volume

Table 2 shows the regression of total motor scores on striatal volumes. Worse total motor score at baseline was associated with smaller striatal volume ($p<0.0001$) and accounted for 15% of the variance in striatal volume.

Table 3 shows the regressions of individual motor domains on striatal volume. Similar to the analysis of probability of diagnosis, worse scores on the bradykinesia and chorea domains were associated with smaller striatal volumes, individually accounting for 11% (bradykinesia) and 7% (chorea) of the variance. Oculomotor abnormalities were more closely associated with smaller striatal volumes than probability of diagnosis and accounted for 9% of variance. These domain-striatum associations were unchanged when a multivariate model was chosen by backward selection. Worse scores on oculomotor ($p=0.005$), bradykinesia ($p<0.0001$) and chorea ($p=0.004$) domains were uniquely associated with smaller striatal volumes.

Table 4 shows the simultaneous multivariate regression of the motor items on striatal volume where the bradykinesia and oculomotor domains are broken into their component motor items. In this analysis, worse scores on saccade velocity, finger tapping, tandem gait and chorea are associated with smaller striatal volumes. The reduced model is similar to the full model with only tongue protrusion additionally emerging as potentially significant ($p = .04$), in addition to saccade velocity ($p=0.0004$), finger tapping ($p=0.001$), tandem gait ($p=0.02$) and chorea ($p=0.003$).

Discussion

In this cross sectional analysis of premanifest HD CAG-expansion-positive participants and expansion-negative controls enrolled in the PREDICT-HD study, total motor ratings distinguished cases from controls. This is despite only slight abnormalities detected on examination in cases (mean total motor of 4.98 +/−5.23 out of a total possible score of 124). These differences appear to be driven largely by the group that was near to their estimated

diagnosis, with the vast majority of other cases having normal to near normal motor examinations. These findings confirm previous smaller studies that have shown that subtle motor abnormalities distinguish expansion positive premanifest HD individuals from controls.[7, 25–27]

Cases with closer estimated proximity to diagnosis had worse total motor scores and worse scores on the motor domains than individuals further from estimated diagnosis. This was most apparent for total motor scores, the chorea domain, the bradykinesia domain and the oculomotor domain. Consistent with our findings is evidence suggesting that chorea[26] and quantitative measures of oculomotility may be sensitive in premanifest HD.[9, 28, 29] Although dystonia was also associated with proximity to diagnosis, it was uncommon in all premanifest groups, consistent with the literature[30]. Although rigidity was not a sensitive measure of premanifest disease in our cohort, it may warrant further investigation in a young-diagnosis sample.[31]

Striatal volumes were smaller in cases than controls, with increasing atrophy associated with closer proximity to diagnosis. This confirms previous findings that striatal atrophy occurs early and may predate diagnosis by years.[14, 32, 33]

Similarly, among premanifest gene expansion carriers, higher (worse) total motor scores at baseline were predictive of a greater probability of diagnosis and smaller striatal volumes. Despite significant univariate relationships between all domains and proximity to diagnosis, however, only worse bradykinesia and chorea domain scores were uniquely associated with a greater probability of diagnosis and smaller striatal volumes. More specifically, chorea and greater impairment on the bradykinesia items of tongue protrusion, finger tapping, and tandem gait were separately associated with a greater probability of diagnosis in cases after accounting for all other aspects of the motor exam. Although the domain score for oculomotor items was not significant, other investigators have purported difficulty with clinically assessing ocular motility[9, 28].

In regards to the association of individual motor items and striatal volumes, only finger tapping and tandem gait (amongst the Bradykinesia items), saccade velocity (amongst the Oculomotor items) and chorea scores were inversely associated with striatal volume. These findings suggest that striatal volumes and probability of diagnosis may reflect slightly different aspects of the motor exam.

Although the sample volunteered from among the population of gene-tested, premanifest persons at risk for HD, there may be a slight selection bias because persons at risk for a young age of diagnosis may be less able to participate. While it may be that younger individuals with earlier diagnosis may be systematically different than the population enrolled in PREDICT-HD, this cohort is similar to the population at-risk and will likely be representative of individuals enrolled in preventive trials. (It is unknown whether data from clinical studies and trials in adults will generalize to the juvenile form of HD.)

A limitation is a lack of prospective validation of diagnosis probabilities derived from the Langbehn et al. formula (or any other HD age-of onset formula). Continued longitudinal assessment of this cohort will ultimately address the validity of the estimated diagnosis formula and the relationship of motor abnormalities to actual disease diagnosis.

In this cross-sectional analysis of the PREDICT cohort, subtle motor abnormalities are present in premanifest HD gene expansion carriers. These motor abnormalities distinguish cases from controls and, among cases, are associated with closer proximity to estimated disease diagnosis and greater striatal atrophy. These findings suggest that the UHDRS motor examination may be a useful outcome measure in clinical trials aimed at delaying diagnosis

of illness (i.e. disease onset) in premanifest HD. Continued longitudinal follow-up of the PREDICT cohort through disease diagnosis will be necessary to better determine which motor domains and items are sensitive to change over time and are predictive of actual diagnosis. Ultimately, multidimensional outcomes including motor, cognitive, behavioral and imaging domains may be necessary in preventive trials.

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Appendix

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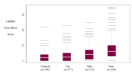

Figure 1.
Total Motor Scores for Controls and Cases by Proximity to Diagnosis*
*p<0.0001 for trend by proximity to diagnosis; Multiple horizontal lines are outlying individual values. The box represent the 25–75 percentile (“inter-quartile”) range. The white stripe in the middle of each box is the median.

Table 1

Baseline Characteristics of the PREDICT-HD Cohort by Gene Status and Proximity to Diagnosis.

Variable	Controls (n=196)	Cases				p-value for cases vs. controls	p-value for trend for cases by far, mid and near diagnosis categories
		Far (n=277)	Mid (n=272)	Near (n=184)	All (n=733)		
Male Gender (%)	62 (32%)	90 (32%)	103(38.%)	77 (42%)	270 (37%)	0.24	0.04
Age (sd)	43.91 (11.37)	36.85 (8.02)	42.30 (9.94)	44.74 (10.24)	40.85 (9.88)	0.0008	<0.0001
CAG repeat length (sd)	19.98 (3.52)	41.14 (1.61)	42.68 (2.18)	44.34 (3.09)	42.52 (2.58)	<0.0001	<0.0001
Parental age of diagnosis (sd)	44.03 (11.18)	50.21 (10.21)	49.40 (10.8)	47.21 (11.25)	49.15 (10.75)	<0.0001	0.015
UHDRS total motor (sd)	2.41 (3.06)	3.47 (3.79)	4.72 (4.79)	7.80 (6.74)	5.02 (5.31)	<0.0001	<0.0001
UHDRS chorea* (sd)	0.27 (0.77)	0.62 (1.26)	0.92 (1.57)	1.59 (2.30)	0.97 (1.73)	<0.0001	<0.0001
UHDRS dystonia* (sd)	0.03 (0.19)	0.06 (0.30)	0.07 (0.34)	0.22 (0.78)	0.10 (0.48)	0.0005	0.001
UHDRS rigidity* (sd)	0.25 (0.61)	0.34 (0.70)	0.32 (0.69)	0.36 (0.78)	0.34 (0.72)	0.08	0.79
UHDRS bradykinesia* (sd)	1.24 (1.79)	1.33 (1.76)	2.03 (2.23)	3.22 (3.02)	2.07 (2.41)	<0.0001	<0.0001
UHDRS oculomotor* (sd)	0.62 (1.28)	1.12 (1.88)	1.38 (2.11)	2.41 (2.65)	1.54 (2.24)	<0.0001	<0.0001
Total striatal volume† (sd)	1.07 (0.10)	1.02 (0.12)	0.92 (0.13)	0.78 (0.14)	0.92 (0.16)	<0.0001	<0.0001
Probability of 5 year diagnosis (sd)	N/A	0.05 (0.03)	0.20 (0.07)	0.45 (0.11)	0.20 (0.17)	<0.0001	<0.0001

*Domains based on factors by Marder et al. (2000).(19)

†Volumetric MRI presented as a % of intracranial volume, n=500 Cases (Far=174, Mid=172, Near=132) and n=149 Controls.

sd=standard deviation

Table 2

Relationship of Total Motor UHDRS to Probability of Diagnosis (n=732) and Striatal Volumes (n=500) in Cases*

Variable	Parameter Estimate (Standard Error)	Partial R^2	p-value
Probability of diagnosis	0.011 (0.001)	0.15	<0.0001
Total striatal volume†	−0.010 (0.001)	0.15	<0.0001

*Controlling for Age and Gender in the linear regression model

†Percent of total of intracranial volume

Table 3

Relationship of UHDRS Motor Domains* and Probability of Diagnosis and Striatal Volumes in Cases.‡

	Probability of diagnosis		Striatal Volume†	
Variable	**Partial R2ψ (n=732)**	**p-value**	**Partial R2ψ (n=490)**	**p-value**
Oculomotor	0.07	<0.0001	0.09	<0.0001
Bradykinesia	0.14	<0.0001	0.11	<0.0001
Rigidity	0.01	0.05	0.01	0.02
Dystonia	0.02	0.0001	0.02	0.002
Chorea	0.06	<0.0001	0.07	<0.0001

*Groupings based on factors by Marder et al. (2000).(19)

‡Controlling for age and gender in the model.

†Percent of total of intracranial volume.

ψConsidering variables one at a time controlling for age and gender.

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Table 4

Relationship of Individual UHDRS Motor Items and Probability of Diagnosis and Striatal Volumes in Cases.*

Variable		Probability of diagnosis			Striatal Volumes†		
		Parameter Estimate (× 1000)	SE (× 1000)	p-value	Parameter Estimate (×1000)	SE (×1000)	p-value
Intercept		−86.79	24.93	0.0005	1148.37	30.77	<.0001
Age (years)		6.07	0.56	<.0001	−50.00	0.68	<.0001
Gender (f vs m)		−24.84	11.14	0.03	50.76	13.31	0.0002
Oculomotor	Pursuits	−18.55	7.48	0.01	−3.06	8.65	0.72
	Saccade Initiation	19.11	5.76	0.001	1.37	7.12	0.85
	Saccade Velocity	3.89	8.49	0.65	−31.97	10.29	0.002
Bradykinesia	Dysarthria	43.16	33.66	0.20	2.46	42.18	0.95
	Tongue	−15.16	18.21	0.41	−32.57	19.19	0.09
	Finger Taps	35.06	7.23	<.0001	−21.66	9.07	0.02
	RAM	5.2	9.18	0.57	−5.08	10.59	0.63
	Luria	21.69	7.19	0.003	−5.85	9.01	0.52
	Gait	52.76	27.77	0.06	−16.16	30.85	0.60
	Tandem	61.43	13.51	<.0001	−35.5	15.96	0.03
	Pull Test	−21.32	11.64	0.07	16.41	14.16	0.25
	Body Bradykinesia	−18.81	15.53	0.23	20.42	20.02	0.31
Rigidity		5.08	7.68	0.51	−9.01	8.68	0.30
Dystonia		10.32	12.06	0.39	−5.74	14.05	0.68
Chorea		9.83	3.43	0.004	−9.83	3.88	0.01

*Controlling for age and gender

†Percent of total of intracranial volume