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Cortical thickness, stance control, and arithmetic skill: An exploratory study in premanifest Huntington disease

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ABSTRACT

Background: Huntington disease (HD) is an inherited neurodegenerative disorder most commonly manifesting in adulthood. Identification of biomarkers tracking neurodegeneration before the onset of motor symptoms is important for future interventional studies. Our study aimed to contribute in the phenotypic characterization of the premanifest HD phase.
Methods: 28 premanifest subjects (preHD), 25 age-matched controls, and 12 manifest HD patients were enrolled for the study. The participants underwent a multimodal protocol including cognitive evaluations, arithmetic ability test, posturography, composite cerebellar functional test (CCFS), and brain 3T-MRI. PreHD were divided at the group median for predicted years to expected onset into "far-from-onset" (>15 years, PreHD-far), and "close-to-onset" (≤15 years, preHD-close). Basal ganglia volumes and cortical thickness were computed using FreeSurfer.
Results: PreHD-close showed significantly lower scores than controls in Symbol Digit Modalities Test ($p = 0.017$), Arithmetic subtraction task ($p = 0.04$), and MMSE ($p < 0.006$). At posturography, preHD-close showed increased sway velocity (<0.04) and distance ($p < 0.02$) compared to controls. PreHD-close had reduced striatum and globus pallidus volumes and left occipital cortical thinning compared to controls. Compared to PreHD far-from-onset, PreHD-close showed bilateral cortical thinning in occipital and parahippocampal regions, inversely correlating with burden score and prognostic index for HD. CCFS only differed between controls and manifest HD. PreHD far-from-onset did not show significant differences in comparison with controls.
Conclusions: We confirmed that quantitative brain MRI represents a valid biomarker of neurodegeneration in preHD. Posturography and Arithmentic tests seem promising tools for detecting early changes in premanifest HD, but need to be further confirmed in large cohorts.

1. Introduction

Huntington disease (HD) is an autosomal dominant inherited disorder most commonly manifesting in mid-life and caused by a pathogenic CAG expansion (>35) in the *HTT* gene. HD patients manifest a complex phenotype characterized by progressive motor,

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behavioral and cognitive abnormalities. CAG repeat length is the major determinant for the age of onset, with larger expansions being associated with earlier onset.

HD mutation carriers usually remain free from symptoms for a few decades before disease manifestation, and this stage is defined as “premanifest phase”. Since the standard neurological exam may be unremarkable in this phase, an increasing number of quantitative clinical and neuroimaging tools have been validated to detect and measure early signs of neurodegeneration. These studies demonstrated that striatal atrophy is one of the earliest and most consistent markers of nervous system changes in premanifest HD subjects (preHD), and that several clinical, cognitive, and motor tasks may be useful in tracking disease progression a few decades before motor onset [1–5].

In the present study we investigated a group of preHD subjects, as compared to controls and early-stage manifest HD, using a multimodal protocol including well-established clinical and neuroimaging tools and a number of relatively new quantitative tasks evaluating stance control, arithmetic ability, and upper limb coordination. The Arithmetic test has been developed to measure striatal dysfunction in combinatorial rule application in the early stages of Huntington disease, and it has not been tested in the preHD [6]. Quantification of upper limb coordination has been used in different movement disorders, but not yet in HD [7]. Our aim was to contribute in the fine phenotypic characterization of a cohort of preHD subjects presenting a wide range of estimated years to motor onset.

2. Methods

2.1. Participants

We consecutively recruited 28 preHD. Inclusion criteria were: age $\geq$18; CAG $\geq$40; Unified HD Rating Scale total motor score (UHDRS-TMS) $\leq$5; Diagnostic Confidence Level (DCL) <2. Estimated age of motor onset was obtained with the model of Langbehn et al. (mean age [CAG] = 21.54 + Exp (9.556−0.1460CAG) [8]. Burden score and prognostic index (PIN_{HD}) were calculated [9,10]. PreHD subjects were divided at the group median for predicted years to expected onset (=15 years). PreHD presenting >15 years from estimated onset were classified as “PreHD-far” (n = 15), and preHD with $\leq$15 years to onset as “preHD-close” (n = 13).

For comparison, we enrolled twenty-five age-matched controls and twelve manifest HD patients. Inclusion criteria for manifest HD were: CAG$\geq$40; UHDRS-TMS >5; UHDRS-total functional capacity score (UHDRS-TFC) $\geq$7 (disease stages I and II); DCL = 4. Six manifest HD were taking antidepressant and/or antipsychotic medications, and three tetrabenazine.

The study was approved by the local ethic committee and written informed consent was obtained from all study participants.

2.2. Clinical and cognitive evaluations

Subjects were evaluated by expert neurologists and neuropsychologists certified as UHDRS-TMS and cognitive raters (http://www.euro-hd.net). The cognitive evaluation included: the Stroop test, the Phonemic and Semantic Verbal Fluency tests, the Symbol Digit Modalities Test (SDMT), the Trail Making Test (TMT) (parts A and B), the Mini Mental State Examination (MMSE) and the Arithmetic task. This latter test consists of 10 simple multiplications and 10 subtractions with carry over. Subjects were not asked to calculate the result but to indicate the correctness of the given solution (half of them had an incorrect result). Only yes/no responses were expected and time was limited to 10 min [6].

2.3. Posturography and composite cerebellar functional severity (CCFS) score

To evaluate possible subtle motor defects in preHD we used the following quantitative tests: 1) the CCFS score computing the nine-hole pegboard and the click tapping tests for the evaluation of upper limb coordination [7]; 2) the posturography assessing stance control with a stabilometric platform (Kistler, CH; acquisition frequency: 500 Hz), as previously described [11]. Briefly, the subjects were instructed to maintain an upright standing natural position for 20 s, barefoot, both with yes open (EO) and closed (EC). The following postural parameters were computed: (a) the length of displacement of the center of mass (COM) (i.e. “distance”; mm); (b) the “velocity” of COM displacement (mm/s); (c) the “surface” (mm^2) of the ellipsoid area, which covers the 85.4% of the COM locations during the tasks. Each parameter was normalized to subjects' height.

2.4. Volumetric and structural MRI data acquisition

Subjects underwent MRI on a Philips Achieva 3T-scanner. The MRI protocol included: high-resolution volumetric T1-weighted sequence (FFE, 240 sagittal slices, TR = 9.9 ms, TE = 4.6 ms, matrix 240 × 240, voxel size = 1 × 1 × 1 mm^3, flip angle = 8°); volumetric T2-weighted sequence (FS, 200 axial slices, TR = 2500 ms, TE = 243 ms, matrix 256 × 256, voxel size = 0.93 × 0.93 × 1 mm^3); and T2 FLAIR (300 sagittal slices, TR = 8000 ms, TE = 331 ms, TI = 2400 ms, matrix 576 × 576, voxel size = 0.43 × 0.43 × 1.2 mm^3).

Subcortical volumetric segmentation was performed on T1 volumes using the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/). An experienced neurologist and biomedical engineer, blinded to clinical and genetic status, reviewed cortical surface reconstruction and subcortical segmentation. Left and right volumes were summed to calculate caudate, putamen and globus pallidus nuclei total volumes, which were then expressed as percentage of the total intracranial volume (TIV).

2.5. Statistical analysis

To investigate the differences in cognitive, postural and volumetric MRI data between the groups we performed the nonparametric Kruskal-Wallis test followed by the post-hoc Steel-Dwass test correcting for multiple comparisons (significance threshold $p < 0.05$). The variable “group” had always four levels (controls, preHD-far, preHD-close, and manifest HD), thus the post-hoc analysis considered a correction for six pair comparisons. Since the effect of groups could be in some cases dependent on age, we also used a linear regression model with age as covariate. Correlations with burden score and with PIN_{HD} were performed using the nonparametric Spearman test. Vertex-wise analyses were used to assess differences in cortical thickness between groups by using a general linear model as implemented in FreeSurfer. Maps showing differences in vertex-wise cortical thickness between groups, and vertex-wise correlation analyses with burden score, PIN_{HD} and SDMT score were all corrected for multiple comparisons after Montecarlo simulation ($p < 0.05$).

3. Results

3.1. Participants

We enrolled 28 preHD (15 men, age 36 ± 10, range 20–55, mean estimated years-to-onset 15.4, range 2–29) and 25 controls (11 men, mean age 3 ± 8, range 21–56, CAG $\leq$35). PreHD and controls

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