Movement Disorders
CLINICAL PRACTICE
LETTER: NEW OBSERVATION

Serum Neurofilament Light and Clinical Biomarkers for Disease Staging in Huntington's Disease

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Recently, the Huntington's Disease (HD) Integrated Staging System (HD-ISS) was developed as a new framework to standardize clinical research for HD.[1] Nevertheless, HD patients can show variable performance in certain tests at a particular visit, therefore not always consistently meeting the criteria for one or the other disease stage. This also includes the prediction of onset and severity of HD in premotor individuals. In this study (local ethics committee approval: AN1979 336/4.19401/5.10, 4464a), we aimed to better characterize biomarker changes in different disease stages of HD, including serum neurofilament light (sNFL) and clinical biomarkers including olfaction and cognitive tests. To this end, genetically confirmed HD patients (n = 54) and premotor HD mutation carriers (preHD; n = 19; ie, without distinct motor symptoms) were consecutively recruited during their routine follow up visits. Results were compared with HD-unaffected participants (healthy controls, HC). Group comparisons of demographic and all clinical as well as sNFL levels are summarized in the supplementary material. We found significant differences between controls and preHD participants in sNfL levels and odor identification, but no difference in cognitive tasks. preHD near to estimated disease onset (NEAR-preHD) based on group median for years to predicted disease onset age using a universal prediction model,[2] but not preHD far to estimated disease onset (FAR-preHD) showed significantly higher sNfL levels compared to HC. Results on cognitive tasks, olfactory functioning and sNfL significantly correlated with the Prognostic Index for Huntington's Disease (PIHD; or its normed version PINHD) PIN_{HD} score (see supplementary material), indicating neurobiological changes with disease progression.

Recently, the relationship between sNfL and CAG repeat length was studied in HD mutation carriers in various disease stages.[3] Moreover, different plasma NfL levels have been reported across all HD-ISS stages with approximately 50% of stage 1 participants having plasma NfL levels indicative of predicted clinical motor diagnosis.[4]

Apart from the association between sNfL and both PIN_{HD} scores and odor identification, we showed that NEAR-preHD, but not FAR-preHD participants, had significantly higher sNfL levels than HC. However, the small sample size should be considered when interpreting our results, which need to be replicated in a larger cohorts. Early deficits on olfaction have already been shown in different neurodegenerative disorders including HD, and former studies assessing cognition and olfaction in HD showed that olfactory recognition is more affected than visual or verbal recognition, possibly because odor memory paradigms depend on a various number of functions (ie, working memory) which may be comprised early in HD.[5] In line with this, we found worse odor identification but no differences in cognitive tests between preHD carriers compared with HC.

These results of relatively unaffected cognition compared to HC but hyposmia could also be explained by the early disease stages of the preHD participants included in our study as well as the small sample size. Our results suggest that olfactory function may be indicative of underlying neurobiological changes in very early disease stages, prior to cognitive dysfunction.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

B.H.: 1A, 1B, 1C, 2A, 2B, 3B
E.M.: 1B, 1C, 2C, 3B
A.B.: 1C, 3B
A.G.: 1B, 1C, 2C, 3B
M.P.: 1B, 1C, 2C, 3B
D.V.: 1B, 1C, 2C, 3B
F.C.: 1B, 1C, 2C, 3A, 3B
A.D.: 1B, 1C, 2C, 3A, 3B
P.M.: 1B, 1C, 2C, 3B
M.K.: 1A, 2B, 2C, 3B
F.K.: 2A, 2B, 2C, 3B
K.S.: 1A, 1B, 1C, 2A, 2B, 3A, 3B

Disclosures

Ethical Compliance Statement: The study protocol was approved by the local ethics committees. All participants gave written informed consent prior to their participation. The interviews and examinations were carried out in accordance with the principles expressed in the Declaration of Helsinki. On behalf of all co-authors, the first and corresponding author confirm that all authors have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1. Demographic characteristics and results for olfaction and sNfL compared between groups.

Table S2. Results of cognitive tests compared between groups.

Table S3. Multiple linear regression analysis (sensitivity analysis*): sNfL levels and odor identification related to PIN_{HD}.

Table S4. Partial Spearman rank correlation between PIN_{HD} and clinical parameters, corrected for age.