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Improving the Clinical Diagnostic Criteria for Genetically Confirmed Adult-Onset Huntington Disease

Considering Nonmotor Presentations

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Abstract

Background

Huntington disease (HD) is a genetic neurodegenerative disorder. Given the focus on motor manifestations, nonmotor symptoms are frequently underappreciated in clinical evaluations, despite frequently contributing to primary functional impairment.

Recent Findings

A diagnosis of motor-onset as the definition of manifest symptoms misrepresents the complex nature of HD presentation. Despite recent attempt to integrate nonmotor diagnostic criteria, practical guidelines are necessary to inform clinical diagnosis. We propose an HD diagnostic framework and staging system that prioritizes genetic testing, integrates motor and nonmotor symptom considerations in the determination of clinical disease onset and severity, and acknowledges the secondary role of clinically indicated diagnostic assessments, incorporating the broad symptom profiles observed in clinical practice.

Implications for Practice

The proposed diagnostic criteria more accurately reflect the presentation of HD and provide greater opportunities for health care professionals to provide appropriate clinical care guidelines for adults with gene-expanded HD.

Introduction

Huntington disease (HD) onset is traditionally marked by distinctive motor signs in genetic carriers, yet alterations in brain structure, biofluid markers, and nonmotor manifestations (cognitive, behavioral, and psychiatric) may precede motor symptoms by years.[1] Additional nonmotor symptoms such as sleep-wake disturbance, pain, autonomic dysfunction, and weight loss contribute to disease morbidity.[2] This sentiment is echoed in recent patient-engagement strategies (e.g., WeHaveAFace.org), where a significant number of respondents

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highlighted the need for guidelines that consider nonmotor presentations of HD. The HD community is actively seeking a diagnostic framework that accurately reflects both clinical observations and patient experiences. Revising clinical diagnosis to reflect nonmotor manifestations of HD is not just important for clinical practice, but it has been requested and is deemed crucial within the patient community. Such revisions include a number of specific benefits: (1) non motor diagnosis will enable better access to social structures such as disability or work-related accommodations; (2) validation to patients and family members that clinical symptoms are consistent with a diagnosis of HD; (3) improved and optimized clinical follow-up that focuses on germane clinical symptom related to HD; (4) better characterization of complex presentations of symptoms within a patient given the heterogenous nature of HD; (5) elevated the need for nonmotor therapies that target cognitive and behavioral symptoms; and (6) earlier access to disease-modifying therapies contingent on symptom presentation for inclusion in clinical trials. Here, we propose how nonmotor manifestations may be considered as diagnostic criteria in HD.

Revising Current Diagnostic Practice

Currently, the clinical diagnosis of HD requires the presence of motor symptoms with a diagnostic confidence level (DCL) of ≥99% specificity for HD etiology.[3] The DCL is based on a global impression from a standardized motor examination, family history, and diagnostic assessments. Empirically, the DCL has been demonstrated to be an inaccurate method to determine phenoconversion.[4] Three broad limitations arise from this approach. First, restricting diagnostic criteria to the motor domain without allowing consideration of nonmotor symptoms delays diagnosis in patients without a prominent motor phenotype pathognomonic of HD. Since hyperkinetic movements are not specific to HD,[5] mild motor symptoms assessed in isolation may increase the clinical diagnostic opinion. Second, many patients with HD experience nonmotor symptoms with associated functional decline arising before motor symptoms.[6] Even when genetic status is established, the accurate diagnosis of HD is delayed for patients with nonmotor predominant phenotypes. This delay has critical implications for patients and families who are seeking treatments and clinical care.

The degree of incremental diagnostic utility in considering nonmotor symptoms in the context of a patient with known CAG expansion with minimal or no motor symptoms depends on the prodromal point prevalence and specificity to HD pathology (as compared with occurrence of similar syndromes in the non-HD genetic carrier population; see Table). Models have been proposed to integrate nonmotor symptoms in other neurodegenerative motor disease, such as an algorithmic approach in Parkinson disease (PD).[7] However, most neurodegenerative populations differ from HD in that a fully penetrant genetic HD diagnosis substantially increases the likelihood of an emergent neurobehavioral syndrome being attributable to HD pathology. The clinical

Table Neuropsychiatric Syndrome Prevalence Rates in Huntington Disease (HD) and General Population

Neuropsychiatric syndrome	HD prevalence Range estimates[13,14]	General population 12-mo prevalence range estimates[a]	Prevalence ratio (odds ratio)
Depression	40–50%	MDD: 7%	5.7–7.1 (10.9)
Apathy	34–76%	PDD: 2.5%	13.6–30.4 (47.7)
Irritability/aggression	22–73%	IED: 2.5%	8.8–29.2 (35.3)
Mania	5–10%	BD: 1.5%	3.3–6.7 (5.3)
Obsession/compulsion	7–50%	OCD: 1.2%	5.8–41.7 (32.8)
Psychosis	3–17%	Schz: 0.3–0.7%	4.3–56.7 (22.1)
Anxiety	13–71%	GAD: 3%	4.3–23.7 (23.4)
Sleep/circadian	90%	Ins: 6–10%	9-15 (103.5)
Cognitive impairment	20–40%	MCI: 2–10% Neuropsych: 6.5%	MCI: 2–20 (6.7) Neuropsych: 3.1–6.2 (6.2)
Suicidality	Ideation: 9–22% Attempts: 7–10%	Ideation: 9% Attempts: 2.5%	Ideation: 1–2.4 (1.9) attempts: 2.8–4 (3.6)

Abbreviations: BD = bipolar I + bipolar II disorder; GAD = generalized anxiety disorder; IED = intermittent explosive disorder; Ins = insomnia; MCI = mild neurocognitive disorder in >65 year olds; MDD = major depressive disorder; PDD = persistent depressive disorder (includes dysthymia and chronic MDD); Schz = schizophrenia spectrum + other psychotic disorders; Neuropsych = <1.5 performance on neuropsychometric testing compared with the normative reference group.

[a] DSM-5-TR diagnoses selected for comparison purposes.[20]

Prevalence ratio (PR) indicates how many times more common a syndrome is in HD compared with a primary psychiatric disorder syndrome in the general population. Odds ratio (OR) represents the increased odds of having a syndrome in HD vs a primary psychiatric disorder syndrome in the general population. Higher values for both PR and OR suggest a stronger association between the syndrome and HD, potentially indicating a higher likelihood that the syndrome is attributable to HD etiology in known gene carriers.

diagnostic approach should reflect this increased level of confidence for attribution of nonmotor neurobehavioral symptoms to HD pathology. Recent work proposed a framework for diagnosing a prodromal behavioral variant frontotemporal dementia (FTD).[8] However, the proposed prodrome of behavioral variant FTD (bvFTD) was criterion-keyed to high risk for conversion to full cognitive and behavioral diagnostic criteria of bvFTD proper. Prior approaches for defining and diagnosing a prodromal HD have criterion-keyed to high risk for conversion into "motor manifestation." An updated clinical diagnostic framework for HD should incorporate nonmotor symptoms in the presence of a known expanded repeat as sufficient for diagnosing the clinical onset of symptoms favored to reflect underlying HD-related neuropathology, rather than confined to a "pre-manifest" categorization.

Cognitive impairment is considered the most common, specific nonmotor feature in HD patients without a prominent motor phenotype. Previous studies estimate of ~10% of patients initially present with cognitive symptoms alone, and 20–40% with both cognitive and motor symptoms.[9,10] In addition to executive-predominant cognitive deficits, difficulties with social-cognition processes can often be identified in early-stage patients, and sometimes even in those gene carriers without visible motor symptoms.[11] Psychiatric presentations are documented in more than half of patients eventually diagnosed with HD, representing an example of high prodromal point prevalence with a varying degree of specificity compared with primary psychiatric disorder prevalence in the general population.[12] Other psychiatric phenotypes such as moderate-to-severe irritability and aggression, mania (5%–20%), obsessive-compulsive features (~20%–50%), psychosis, and suicidal ideation or behaviors (~10%–20%) occur at a lower prevalence but are more specific to patients with HD than general population base rates.[13,14] Behavioral dysregulation syndromes such as apathy, disinhibition, and risk-taking behavior have been documented to precede motor symptoms in ~30%–40% of HD genetic carriers.[15,16] Apathy is the most commonly reported behavioral symptoms in HD and has been shown to correlate with degree of caudate atrophy before the onset of motor symptoms.[17,18] These symptoms are suggested to represent an intermediate level of specificity compared with general population incidence, though deserve consideration in making a nonmotor diagnosis. Finally, nonmotor symptoms that range from pain, to sleep dysfunction, and digestive disorders, are commonly encountered in HD, but these symptoms are not always appreciated in the diagnostic criteria and can be encountered in non-HD pathologies.[19] Table provides a summary of reported prevalence rates for neuropsychiatric syndromes in both nonmotor and motor manifest HD, in contrast to significantly lower 12-month prevalence rates for primary psychiatric disorder equivalents. Although there are insufficient empirical data to confidently provide prevalence rates for neuropsychiatric syndromes in nonmotor gene expanded patients with HD, this summary is intended to support the importance of considering HD as an etiology for cognitive, behavioral, and affective/emotional symptoms in gene expanded patients, especially when the symptoms are persistent and/or multiple syndromes are present.

As such, nonmotor symptoms are highly relevant given their impact on everyday function and quality of life. For many patients, these symptoms may be greater than that posed by motor symptoms alone.[11] Integration of informant-reported symptoms and functional problems may be critical for diagnosis in many patients with HD, due to reduced insight of clinical symptoms.[21]

Given the varying degree of nonmotor symptom specificity to HD pathology, integration of nonmotor symptoms into the HD diagnostic process requires a comprehensive assessment catered to the individual symptom presentation (e.g., *if clinically indicated*: neuroimaging, blood/CSF lab analyses, neuropsychological evaluation, and autonomic functioning testing may be indicated). This use of an integrated multidisciplinary assessment to determine a global clinical presentation representing HD pathology contrasts with recently proposed research criteria (Integrated Staging System [ISS]).[22] The ISS incorporates narrow and specific MRI biomarker findings and a single cognitive test as criteria for related disease stages; however, a flexible, patient-focused, clinical approach is necessary for an integrated diagnostic opinion. Recent proposals for nonmotor diagnostic criteria[23-25] represent steps in the right direction but tend toward disproportionate focus on cognitive impairment and/or continue to rely on integration of DCLs. The following proposal is intended to build on these advances, toward updated recommendations for a clinical diagnostic process for HD.

Proposed Diagnostic Practice

Principles

The following principles guide the diagnostic procedures of HD:

1. The fundamental diagnostic test for HD is the molecular genetic test of the CAG repeat in the HTT gene. The diagnosis of HD has broad implications to a patient and family. Whenever possible, international guidelines for presymptomatic genetic testing should be followed, integrating genetic counselling incorporating a mental health assessment. Clinically motivated genetic testing should similarly integrate a genetic counselor whenever possible, or an equivalent subject matter expert in settings where such a resource is not feasible.
2. Clinical diagnosis of symptomatic HD requires assessing both motor and nonmotor symptoms. In at-risk patients who present with HD-related symptoms, symptomatic pretesting counseling should review clinical implications should the genetic diagnosis be confirmed. When

symptoms are linked to another medical condition, the diagnostic process should encompass neuropsychological testing, neuroimaging, laboratory assessments, and ancillary tests to gauge the likelihood of a non-HD diagnosis.[26] The intricate nature of this determination may necessitate a multispecialist consultation in cases of nonmotor or unclear phenotypic presentation.

Interpretation of Genetic Testing

Full-penetrance HD causing alleles are defined as CAG repeats of 40 and above and associated with clinical manifestation of disease assuming a normal lifespan, with reduced-penetrance HD causing alleles defined as 36–39 CAG repeats and associated with increased risk of clinical manifestation of disease.[27] An unaffected range of CAG repeats is defined as 26 or fewer CAG repeats. An intermediate range of 27–35 CAG repeats imparts increased risk of offspring inheriting a penetrant allele due to instability in CAG tract. There have been case reports of HD-like symptoms in this patient population, but at present, evidence to associate intermediate range repeats with risk of developing an HD phenotype is limited; thus, further research on other factors is required before assigning a probable association between the intermediate range CAG repeat genotype and a clinical HD diagnosis.

Proposed Clinical Diagnostic Criteria for Genetically Confirmed Adult-Onset HD

We propose staging criteria based on the clinical assessment of nonmotor symptoms in adult patients with abnormal CAG repeats, i.e., greater than 36, in the absence of unequivocal motor signs of HD (see Figure for examples of clinical presentations and considerations). Existing motor sign diagnostic criteria for HD diagnosis remain, but in the absence of such, these criteria provide for a means of clinical diagnosis of symptomatic HD based on clinical assessment, management, and longitudinal monitoring of nonmotor symptoms. Of nonmotor symptoms, particular attention is given to cognitive, behavioral, and affective symptoms that may interact and reflect recognized neuropsychiatric syndromes, although ancillary and aggravating symptoms may be considered (e.g., metabolic and autonomic). Additional clinically indicated medical diagnostics should inform the attribution of symptoms to HD pathology and exclude competing alternative diagnostic conditions.

1. Asymptomatic HD:
   a. CAG expansion confirmed.
   b. Absence of neurologic symptoms/signs and/or neurobehavioral syndromes.
2. Possible symptomatic HD:
   a. CAG expansion confirmed.
   b. Absence of unequivocal motor signs of HD on neurologic examination.
   c. Presence of nonmotor neurologic symptoms/signs and/or neuropsychiatric syndrome(s) that are
      i. Evident on initial clinical assessment.*
      ii. Change from baseline and persistent/recurrent per history (patient/informant).
      iii. Not better accounted for by alternative neurodegenerative diseases, nondegenerative medical disorders, or primary psychiatric diagnoses.#
3. Probable symptomatic HD:
   a. CAG expansion confirmed.
   b. Absence of unequivocal motor signs of HD on neurologic examination.
   c. Presence of nonmotor neurologic symptoms/signs and/or neuropsychiatric syndrome(s) that are
      i. Persistent/recurrent or progressive, per longitudinal clinical assessment, despite provision of appropriate clinical management.^
      ii. Not better accounted for by alternative neurodegenerative diseases, nondegenerative medical disorders, or primary psychiatric diagnoses.#

*Per objective assessment measures, e.g., cognitive screen or neuropsychological evaluation (especially if cognitive symptoms are sole clinical feature), psychometrically validated symptom reports from patient and/or informant.[27]

Clinically indicated medical diagnostics should be used to exclude alternative diagnoses.

^Longitudinal clinical assessment recommended over 3–12 months, or, sufficient time for therapeutic response to the clinical management provided.

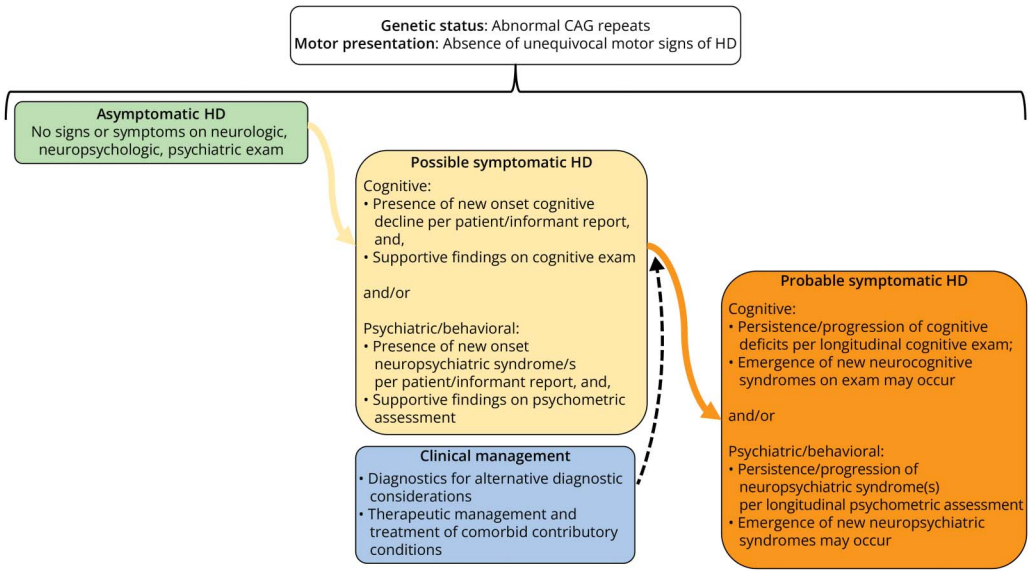
Future Directions

The presence of *equivocal* motor symptoms/signs of HD is not considered as a criteria for delineating possible vs probable symptomatic HD in this proposal. In addition, aside from comment on the prototypicality of a dysexecutive neurocognitive syndrome in HD, a hierarchy of neuropsychiatric syndromes is not proposed. These decisions were based on the current lack of sufficient empirical evidence to operationalize into clinical practice. Rather, longitudinal objective clinical assessment of nonmotor symptoms is emphasized for this diagnostic differentiation. Furthermore, these proposed criteria do not incorporate functional effect of symptoms, which is better suited for disease severity staging. Future revisions to these clinical diagnostic criteria may incorporate these considerations, if supported by empirical findings and professional consensus.

Recent advances in nongenetic biomarker diagnostics for HD have been integrated into research criteria, with provision for empirically based refinement in the future.[22] These clinical diagnostic criteria should accommodate potential future integration of neuroimaging, neurophysiologic, and molecular biomarkers, pending sufficient empirical validation and broad community access.

These diagnostic criteria are not designed to diagnose juvenile HD (jHD). Diagnosing and managing jHD involves unique

Figure Clinical Diagnosis of Genetically Confirmed Adult-Onset Huntington Disease



Proposed symptomatic categories for patients with abnormal CAG expansion and the absence of unequivocal motor signs of Huntington disease (HD).

considerations due to the differences in symptomatology and disease progression compared with adult-onset HD.[28] Recognizing these distinctions, we advocate for the development of a separate, comprehensive diagnostic proposal tailored specifically for jHD. This specialized framework would address the unique challenges and clinical features associated with juvenile HD.

Practical Implications

The complexity of HD emphasizes the need to take a broad range of evidence into account, including the input of family members and those close to the person with HD. Since HD presents with variable motor, cognitive, behavioral, psychiatric, and ancillary symptoms at different times in life, integrated multidisciplinary clinical assessment should be integrated with genetic testing when diagnosing HD. Additional neurobehavioral workup is important to rule out alternative etiologies and help identify comorbidities that require treatment whether HD related or not. *One intended consequence of these diagnostic criteria is the possibility of a diagnosis of symptomatic HD in a confirmed genetic carrier adult without the presence of motor signs.* The functional effect of the heterogenous symptoms of HD is an important aspect of clinically staging. These proposed clinical diagnostic criteria better capture the empirically demonstrated natural course of HD pathology, facilitate improved clinical management, and access to social/legal supports across the disease spectrum, will improve clinical research methodology and is capable of integrating resultant incremental refinement, and would offer improved access to any eventual premanifest disease-modifying interventions. Their final advantage is that in addition to being grounded in clinical experience, they adopt a more rounded perspective on the impact of HD, as requested by, and informed through, individuals directly affected by HD.

Author Contributions

C.M. Considine: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. C.M. Eddy: drafting/revision of the manuscript for content, including medical writing for content. S.A. Frank: drafting/revision of the manuscript for content, including medical writing for content. S.K. Kostyk: drafting/revision of the manuscript for content, including medical writing for content. M. Oosterloo: drafting/revision of the manuscript for content, including medical writing for content. A. Killoran: drafting/revision of the manuscript for content, including medical writing for content. E. Furr Stimming: drafting/revision of the manuscript for content, including medical writing for content. M. Dose: drafting/revision of the manuscript for content, including medical writing for content. T. Cruickshank: drafting/revision of the manuscript for content, including medical writing for content. T.D. Bird: drafting/revision of the manuscript for content, including medical writing for content. L. Vetter: drafting/revision of the manuscript for content, including medical writing for content. A. Arnesen: drafting/revision of the manuscript for content, including medical writing for content. J. Valvano: drafting/revision of the manuscript for content, including medical writing for content. H.W. Lange: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. D.O. Claassen: drafting/revision of the manuscript for

TAKE-HOME POINTS

- HD is a neurodegenerative disorder that causes changes in brain metabolism, structure, and function that can be measured/detected years before clinical symptoms or signs appear.
- Currently, the clinical diagnosis of HD requires the presence of motor symptoms ≥99% specific for HD, which may delay diagnosis when less severe motor symptoms are present in the context of supportive nonmotor symptoms, or, when convincing nonmotor symptoms emerge before unequivocal motor signs.
- Despite often causing significant functional impairment in the pre-to-early motor manifest stage of HD, nonmotor symptoms are frequently considered secondary.
- Clinical proposals for nonmotor symptom integration into diagnostic criteria are laudable but have not been as comprehensive (or widely known in the community practice) as research-based systems.
- These proposed new HD diagnostic guidelines integrate nonmotor symptoms of HD into a holistic diagnostic framework for adult gene expanded patients, to more accurately reflect HD pathology progression, enable better clinical treatment, and provide greater chances for interventions during the preclinical phase.

content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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