Tremor and Other Hyperkinetic Movements

Viewpoints

Huntington Disease: The Complexities of Making and Disclosing a Clinical Diagnosis After Premanifest Genetic Testing

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Abstract

The management of patients and families affected by Huntington disease (HD) is complicated by several factors, both practical and ethical. It can be difficult to determine the onset of clinically manifest HD (mHD). In addition, it can be challenging to decide when to disclose the diagnosis to the affected individual. Firstly, the features of HD, an incurable, inherited, neurocognitive disorder that often manifests in young adulthood, influence how the person presents and accepts a diagnosis. Secondly, a positive genetic test for HD may result in a genetic diagnosis, sometimes years before the development of clinical features and the diagnosis of mHD. Thirdly, observational studies of unaffected gene expansion carriers documented HD manifestations up to 10 years before the typical presentation for diagnosis. These developments may permit earlier genetic diagnosis and information regarding the patient's likely status with respect to the development of clinical disease. Making the genetic diagnosis of HD and providing information regarding disease status, earlier rather than later, respects the person's right to know and preserves honesty in the doctor/patient relationship. Conversely, delaying the diagnosis respects the right not to know, avoids potential discrimination, and permits the person to live a "normal" life for longer, in the context of a disease without cure. This discussion has implications for other inherited and neurocognitive disorders.

Introduction

Huntington Disease (HD) is an incurable, inherited, neurocognitive disorder[1,2] with prominent motor manifestations in addition to non-motor changes in behavior and cognition. Depression, unawareness and impulsivity are typical. In HD and many other disorders, a "genetic diagnosis" in an unaffected, premanifest person is possible with genetic testing, years before it is possible to make a diagnosis of clinically manifest HD (mHD). These factors influence how the diagnosis of mHD is made and disclosed. There are many elements to making a clinical diagnosis. These were summarized by the medical philosopher, Spicker, who wrote, "In addition to the acquisition of differential knowledge on the part of a physician, medical diagnosis depends on the subtleties of the patient-physician encounter, the prevailing nosological and conceptual systems in which this encounter occurs, the current status of biomedical research, and the physician's reliance on the accuracy, reliability, and validity of the available laboratory analyses."[3] These concepts are relevant when we deliver information and a diagnosis, including to those with a "genetic diagnosis" before clinical diagnosis. The past 30 years of genetic laboratory technologies resulted in the discovery of the causative genes for roughly half of 7,000 Mendelian disorders, many of which are movement disorders.[4,5] Using HD as an example, we consider the complexities of diagnosis and disclosure in clinical practice in the transition from a genetic diagnosis only, through the disease prodrome, to the diagnosis of mHD.

Conventional clinical diagnosis of disease

In practice, the usual process of disease diagnosis is that the individual describes their symptoms (complaints) to the physician, who elucidates the history; examines the patient; discusses the findings, likely diagnosis and treatment, and the need for further investigation. This process may differ for chronic, incurable, neurological diseases. Those who are unfamiliar with HD, for example, may not realize that diagnosis of mHD and disclosure of diagnosis are best approached in a different manner.

Diagnosis of mHD

In the case of HD, there are features that require caution when a diagnosis is made and disclosed. A diagnosis of mHD is based on history and examination, in particular the presence of chorea. There are, however, many additional aspects to take into consideration. These factors should be contemplated even when the diagnosis is supported by a family history and/or confirmatory genetic testing for a pathologic cytosine-adenine-guanine (CAG) expansion in the huntingtin (HTT) gene and imaging studies.

The unique nature of HD

HD can present in young people with dementia, which is often associated with unawareness and impulsivity; indeed, HD was recently included in the Fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as a neurocognitive disorder.[2,6–8] Patients may not present with symptoms or be aware of changes taking place, including functional impairments and their impact on others, particularly family members. Depression and other behavioral manifestations are common.[1,9] As an inherited and incurable illness, many people observe the devastating effects on their affected family members. The person's reaction to a diagnosis may be unpredictable.

Current diagnostic criteria

The current formal diagnosis of mHD is based only on motor diagnostic criteria that are part of the Unified Huntington Disease Rating Scale (UHDRS).[10] For a diagnosis of mHD, the clinician rates 4 on the 0 to 4 UHDRS Diagnostic Confidence Limits (DCL) scale. This rating, calculated after motor examination, indicates >99% certainty that the rater believes that these motor signs are attributable to mHD. This assessment tool is used in premanifest and other clinical studies, including drug trials. Overall motor abnormalities are rated as the Total Motor Score (TMS). However, there is lack of clarity, as there is no precise threshold on the TMS to define DCL 4, so this rating depends on the rater's expertise. There is a need to review and incorporate the evolving diversity of disease features, taking into account the DSM-5 definition, and to formulate a wider definition of mHD and its prodrome.[2,11,12]

Phenotypic variations in HD presentation

HD has a variable phenotype. Thanks to genetic testing and large observational studies,[13] there is now a better understanding of the possible presentations and natural history of mHD, in addition to appreciation of the initial symptoms and signs.[14–16] Premanifest studies indicate that disease is not always motor at onset. Chorea may be absent and is not essential for clinical diagnosis.[17] For example, depression and apathy are common early manifestations.[9] On rare occasions, psychosis may be the initial presentation. In addition to being common presentations in younger-onset HD, akinetic-rigid and dystonic syndromes may occur in adults.[1] These and other atypical features (e.g., late age of onset) can result in an initial clinical presentation many years beyond the earliest disease manifestations, especially in the absence of a family history.[18,19]

The impact of premanifest studies and earlier diagnosis

It can be postulated that the disease process begins at birth, but clinical signs, and less reliably symptoms, only develop when accumulating pathology impairs neurological function.[20] There is unequivocal evidence that the process of HD begins and progresses before the conventional diagnosis of mHD can be made. Subtle, reproducible imaging and cognitive, behavioral, psychiatric, motor, and functional manifestations are documented 10 to 15 years before the expected motor diagnosis. The principal sources of this information are pivotal longitudinal studies (Predict HD and TRACK HD)[9,14,15] comparing the natural history of premanifest expansion carriers with noncarriers. The PHAROS study[21] of at-risk people with a family history of HD reached similar conclusions. Because of these and other studies, it is apparent that some features might define clinical disease onset much earlier than the current definition of motor onset. These earliest disease manifestations can often be recognized in clinical practice and can lead to earlier diagnosis, as well as to discussion of prodromal manifestations of HD. There are models predicting the likely age of onset based on CAG repeat expansion length; however, these are not sufficiently accurate for use in a clinical setting and are only an approximate guide.[22] It may be possible to use other factors to define onset, and these could be relevant in clinical trials or in initiating a proven, protective, or curative intervention in the future.[23] For example, diagnosis could be based on imaging, along with other subtle motor, behavioral, and cognitive changes. It might also be possible to use a "biomarker" diagnosis of disease onset, if sufficiently accurate (e.g., mutant HTT measurement).[24] With better understanding of the natural history of HD in the premanifest to earliest mHD phase, it would be possible to provide information for potentially affected family members, regarding their risk of disease inheritance and whether they might have prodromal signs prior to a definite diagnosis of mHD.[21]

Some argue that HD be considered as a continuum, avoiding concerns related to fears of a definite point of diagnosis, and with interventions based on functional decline. In addition to these issues, great caution is required when considering how and if this information about the premanifest, prodromal, and earliest disease course is interpreted and disclosed.

Caveats in diagnosing HD

Special attention should be directed to certain aspects of diagnosis and disclosure.

1) Certainty that the manifestations, especially the nonmotor and early manifestations are HD-related cannot be overemphasized. When a parent has HD, each child has a 50% chance of inheriting

the expansion. Those who decide on premanifest testing may receive a genetic diagnosis, sometimes years in advance of onset of mHD. For example, an unaffected 18-year old may be a carrier but have years of fully productive life before any symptoms and signs emerge. During that time, some symptoms and signs could develop that might not be HD-related and be wrongly attributed to mHD, such as thyrotoxicosis with anxiety, tremor, and weight loss. Depression is common in the general population but can also be a prominent manifestation of HD.[9,23] While CAG repeat size does not predict a definitive age of onset, it may provide some guidance. Nonspecific symptoms in a young patient with a reduced penetrance repeat size, and hence an expected late onset of clinical HD, would be unlikely to be attributable to the mutation. Other behavioral changes (e.g., psychosis in an HD family member) may be difficult to attribute to mHD.[25] Treatment with an antipsychotic agent might potentially mask signs of chorea in such a patient.

2) Unawareness is common in HD and can be an early disease feature. Some patients present only when a relative recognizes the signs.[6–8] Recognition can be especially challenging when there is no family history or if there is no caregiver involved. A report from a companion is desirable since their information about disease impact, both social and functional (e.g., in the work place), may be more reliable than self-report.[26] Heightened awareness is a concern. In our experience, this is often a feature of those who commit suicide. Not every patient accepts the diagnosis of HD, especially if they are unaware of the signs of disease.

3) Manifestations may not have functional impacts. Some signs of mHD go unnoticed because there are no associated symptoms or functional effects (e.g., abnormal eye movements and mild chorea).[27] Early signs could be unrecognized because some occupations require fewer cognitive resources or do not depend on fine motor skills.

Advantages of making the diagnosis

There is no cure for HD, but making the diagnosis curtails unnecessary investigations and allows access to care, family support, and education. Many manifestations, notably depression and irritability, are treatable or manageable.[23,28] Most would agree that mHD is best managed by disease-specific services, if available, and before there is irreversible damage to the patient's relationships. It can be argued that the neurologist has a "duty of care," for example, in

Table 1. Reasons for Disclosure vs. Nondisclosure in Giving a Clinical Diagnosis of HD

Reasons for Giving Full Information and an Earlier Diagnosis
- The right to know
- Honesty in the doctor/patient relationship
- Avoidance of paternalism
- Careful but frank discussion of possible place on the disease trajectory, which may (or may not) allay fears that clinical disease will develop imminently
- Opportunity to plan a more sustainable career path as disease progresses
- Opportunity to put affairs in order for the future
- Early engagement may avoid the problems of increasing lack of awareness and inability to recognize the need for future care
- Interventions can be made for early HD manifestations identified in the premanifest/prodromal studies (e.g., depression, irritability, and apathy)
- The potential to reduce irreversible social and personal impact including on the family and caregiver
- Opportunity to involve family members, particularly the genetic family, who arguably have a right to know of their risk
- Adopt a healthy lifestyle with exercise and cognitive training, limited alcohol, and no smoking
- Opportunity for research, including participation in trials in early HD before irreversible pathology accumulates
- Allows access to disease-specific services and care

Reasons for Delaying Information about Earliest Manifestations and Early Diagnosis
- Right not to know
- Fear of discrimination in the workplace and regarding health and other insurance
- Allows a "normal" life for longer
- Avoids a perception of illness ahead of time and a disease "label"
- May avoid anxiety in relation to possible disease onset
- May avoid impacts on personal relationships
- Delays fear associated with diagnosis, especially because of knowledge of affected relatives
- Information extrapolated from research studies, especially prediction of onset from trinucleotide length, may not be accurate for an individual
- Symptoms and signs may not be HD-related

Abbreviation: HD, Huntington Disease.

situations in which there is some urgency to diagnose mHD. Some quite advanced, cognitively impaired, and unaware patients live in dangerous and disadvantaged circumstances that require immediate intervention. While it may be impossible to prevent all behavioral symptoms and risky activities (e.g., unsafe driving and financial misman-agement), a diagnosis and explanation of the manifestations improves understanding, especially for caregivers, as well as alerting them to potential problems that could be avoided. Arguably, the "genetic" family (those family members who may have HD or could inherit the disease) are entitled to know of their risks in a timely manner.[29,30]

Ethical challenges and disclosure

The determination of when to disclose the diagnosis of HD to an individual is a matter of clinical judgement.[2,11] Assessment should include not only the history and HD-specific examination (motor, cognitive, behavioral, functional and social), but also the person's

degree of awareness of disease signs, and their preparedness to accept a diagnosis. This applies especially for the genetically tested, premanifest person who could be relatively unaffected for a number of years. The consequences of giving or not giving an early diagnosis, providing information regarding subtle signs, or an estimate of likely age of onset, must all be considered with great care and sensitivity, while simultaneously respecting the person's autonomy.[31] In addition, whether to discuss clinical manifestations with little or no effect on activities of daily living, with an at-risk or premanifest person, may depend on the person's preferences, if known, and the nature of the therapeutic relationship. The individual may not seek a clinical diagnosis but rather reassurance that they are without signs of mHD. The right to know (autonomy), and alternatively not to know, must be judged against the ethical principles of "do no harm" and "duty of care" (beneficence).[32,33] For example, discussion of signs observed during a research-only visit is usually not permitted in most research

Table 2. Hypothetical Cases and Comments Reflecting the Authors' Experience

Case 1: A middle-aged person carried a mutation of the same length as their father who had late-onset disease. Their occupation required planning and flexibility. The person complained of poor organizational skills at a time when the UHDRS motor score was less than 5. Neuropsychological testing revealed impairment, attributed to depression and anxiety. Brain MRI showed caudate atrophy. A diagnosis made on behavioral and imaging data allowed medical retirement. Definite HD motor signs developed 4 years later, about 20 years younger than the father's age of onset.
Comments: Individual age of disease onset cannot be predicted from the size of the trinucleotide repeat expansion. Other factors likely modify age of onset and variation in families. This person with preserved awareness had an occupation that alerted them to changes. A predominantly nonmotor onset can occur. An early diagnosis before definite motor onset facilitated medical retirement and supported and validated their perceptions of impairment.
Case 2: A person aged 35 presented after the death of their mother following disease onset at age 45 years. They carried the same size trinucleotide expansion. They complained of poor organization, planning and depression impacting on their work. Examination revealed no motor features. The person stopped work to enjoy life. Neuropsychological testing, brain MRI, and PET scans were normal at presentation and at 3-year follow-up.
Comment: A later onset would be more likely. Referral to a psychiatrist allowed assessment of depression. Not all behavioral and psychiatric manifestations are the result of HD, however this may be difficult to determine. Withholding the diagnosis until there is greater certainty that the manifestations are mHD is difficult when the person seeks a diagnosis.
Case 3: A premanifest research participant lives alone and presented alone. They report a high level of functioning, including a job that requires fine motor skills, but lacked awareness of their obvious chorea. For confidentiality reasons, no workplace report is possible. No diagnosis was given, but follow-up was arranged. This person continued to work but did not return to follow-up visits.
Comment: The dilemma is whether to inform a person of the diagnosis when unaware and reporting no difficulty, especially without informant input. Impairment of fine movement may be harmless in some occupations but could have consequences in others that require fine motor skills. Decisions about when and how to disclose the diagnosis are influenced by the degree of risk to the person and others, if this is known. Most research protocols do not allow discussion of clinical manifestations at a research visit.
Case 4: A depressed, at-risk young person whose affected father had onset in his 40s has not undergone genetic testing. They discuss plans for a high-risk career. They are unaware of early signs but ask if there are any changes. Depression was treated, and plans were delayed until review with a companion. The probable early signs were discussed, baseline neuropsychological testing arranged, and ongoing review of depression.
Comment: This situation demonstrates the conflict between "doing no harm" versus "duty of care." It also demonstrates the need for honesty as this person is unlikely to progress in their chosen career. Although difficult to convey, timely diagnosis prevents future distress (e.g., investing in a career path that cannot be fulfilled).

Abbreviations: HD, Huntington Disease; mHD, Manifest HD; MRI, Magnetic Resonance Imaging; PET, Positron Emission Tomography; UHDRS, Unified Huntington Disease Rating Scale.

protocols. The neurologist, or other clinician, has a dilemma of "if and when" to inform the patient, especially if there is no apparent functional impact of delivering the diagnosis, and must weigh the ethical principles involved in knowing and not telling (nondisclosure) versus "telling too soon."[34]

Disclosure of the diagnosis based on nonmanifest features warrants special attention, as these may be common in the general population, (e.g., depression and irritability) but may cause great disability even in early mHD and are treatable.[35] Many of the consequences of earlier diagnosis are similar to those discussed in the premanifest, genetic counselling protocols, and in the reviews of premanifest testing[36,37] (e.g., possible discrimination).[38] In HD, the main focus of discussion has been on the implications of genetic testing and disclosing a genetic diagnosis to an unaffected carrier, rather than the dilemma of diagnosis of mHD and disclosure of this, a difference from Alzheimer disease (AD) and dementia.[34,39–43]

Once a diagnosis is made and disclosed, discrimination may be more likely, especially when the individual seeks insurance. In some countries, legislated protection is afforded (e.g., the Genetic Information Nondiscrimination Act [GINA] in the US).[44] However Green et al.[44] highlight a "gap in protection" between the GINA legislation protecting the individual's genetic information and the Americans with Disabilities Act (ADA), protecting those with manifest disease that limits their ability. On review of the legislation, Green's conclusion was that those with manifest disease but who are not disabled are without protection. Insurers invariably withhold cover for these clinically unaffected years and treat people with varied CAG repeat expansion sizes as having the same prognosis.

Ethical considerations when discussing early findings or giving a diagnosis prior to mHD

Many possible pros and cons of disclosure or nondisclosure need consideration before information is provided regarding the expected age of onset or the earliest signs and diagnosis (see Table 1).

Hypothetical cases and comments

Four hypothetical cases reflect the authors' experience over many years (see Table 2). Recommendations for the HD diagnosis and disclosure process are shown in Table 3.

Other neurocognitive diseases

Many of the ethical challenges encountered in HD are discussed in the considerable literature regarding dementia and especially AD. In AD, there are expanded definitions incorporating recent research into the premanifest/prodromal phase, biomarker and imaging changes, and the diagnosis of mild cognitive impairment.[45,46] In HD, much has been written about the ethical implications of premanifest and even diagnostic testing; however, the dilemmas surrounding mHD diagnosis and disclosure have been relatively neglected compared with other forms of dementia. The difficulties interpreting early imaging and biomarker findings and diagnosis, including the ethics of disclosure and nondisclosure and patient autonomy and unawareness, have been reviewed.[47] Research has been undertaken to determine patient and family opinions about disclosure and nondisclosure, as well as those of health professionals. In their literature review of 47 studies, Werner et al.[42] conclude that "the move between truth telling and being honest

Table 3. Considerations Regarding HD Diagnosis and Disclosure

The following should be considered:
An individualized approach to every patient is essential
What does this person know about HD, and what are their expectations for the future?
What are the person's expectations from the clinic visit?
What support do they have?
A companion's report is valuable, particularly of impact on social and work place function.
The person may not have symptoms or be aware of obvious signs of mHD.
Awareness of signs and disease impact may be linked to adverse outcome (i.e., suicide).
Some signs have no impact on function and go unnoticed.
Look for another explanation as some manifestations are unrelated to mHD (e.g., depression).
In the context of atypical presentations, is onset likely at the particular trinucleotide repeat length?
If unsure, treat the symptom and arrange early review or appropriate referral and follow-up.
Weigh the advantages of an immediate diagnosis and the need for interventions.
Gradual introduction to a definite diagnosis, if this is safe.
What is the impact on others, particularly the family?
Remember the right of genetic family to know their risk in a timely manner.
Discuss future disclosure about mHD, the disease prodrome, and earlier diagnosis after a premanifest genetic test result.
The reaction to disclosure of mHD, and of identifying previously unrecognized prodromal findings, may be unpredictable.

Abbreviations: HD, Huntington Disease; mHD, Manifest HD.

while being sensitive and showing concern to patients' abilities and needs and fear of doing harm is a continuous struggle that no guideline can resolve." They recommend a diagnosis disclosure "process" rather than a diagnosis disclosure "encounter." The autosomal dominant inheritance of HD raises additional issues; however, the dilemmas in dementia diagnosis and disclosure are sufficiently similar to guide further research in HD.

Conclusion

Many factors must be considered when making and disclosing a diagnosis of mHD, but this is especially true when a genetic diagnosis precedes the clinical diagnosis of mHD. For the neurologist or other clinicians in positions of trust, ethical issues are raised when clinical signs of mHD are apparent of which the person is unaware. To our knowledge, this dilemma is not addressed in the HD literature to date, although it has been recognized in AD[34,39–41,46] and in other neurocognitive diseases.

Since identification of the HD mutation over 20 years ago, knowledge of the disease course has greatly improved. Strategies to manage some of the manifestations are possible, even at earlier stages. Genetic testing and research studies allow a better understanding of phenotypic and genotypic variations and the premanifest phase, and this could inform a revised, comprehensive definition of HD. Determining how to apply this updated definition to the individual with their particular symptoms, signs, and perception of HD, in addition to when and if the diagnosis should be delivered, will be paramount. Making a clinical diagnosis of mHD can be a complex process despite the availability of genetic testing. The course of HD is long. Most affected people have many productive years following a premanifest genetic diagnosis or clinical diagnosis and before functional impacts. The complexities arising when a clinical diagnosis of mHD follows genetic diagnosis have implications for other inherited and neurodegenerative diseases.[48]

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