QAs

Huntington Disease

Targeting the Triad

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When should I consider HD in the differential?

A Huntington disease (HD) is a progressive, neurodegenerative disease characterized by a disorder of mood, movement and mentation (Figure 1). It should be considered in any patient presenting with this triad of signs and symptoms.

While median age of onset is 39, the diagnosis has been made at ages ranging from two to over 80 years old. Prevalence is approximately five per 100,000, making it the most common inherited neuropsychiatric disorder.

Does negative family history lead away from a HD diagnosis?

A HD is inherited in an autosomal dominant fashion, with complete penetrance. The mutation causing the disease is a CAG repeat expansion in the coding region of the HD gene; CAG repeats > 35 are associated with disease manifestation, and the repeat length is inversely correlated with age of onset.[1]

Individuals with an "intermediate" allele (CAG 29-35) can pass on a CAG expansion in the disease range (*i.e.*, > 35) due to repeat length instability, especially through the paternal line. This may be the explanation in Harry's case.

Harry's case

- Harry, a 61-year-old GP, presents to his family physician with complaints of "slowed thinking" and difficulty remembering new drugs needed in his practice.
- He is dropping things and his wife notices he makes fidgety movements, particularly while watching sporting events.
- He also complains of poor sleep and diminished interest in his hobbies.
- Harry's parents died in their early 70s, his father of heart disease and his mother of breast cancer.
- He has no siblings and has little contact with his paternal aunts, uncles and cousins, as they live in Russia.
- No one on his mother's family has had dementia or a movement disorder.

Harry's exam results

- He scores 30 on the mini-mental status exam.
- Ocular pursuits are jerky.
- Finger tapping and rapid alternating movements are slowed.
- Tandem walk is wobbly.
- Small amplitude choreic movements are noted intermittently in the distal extremities.

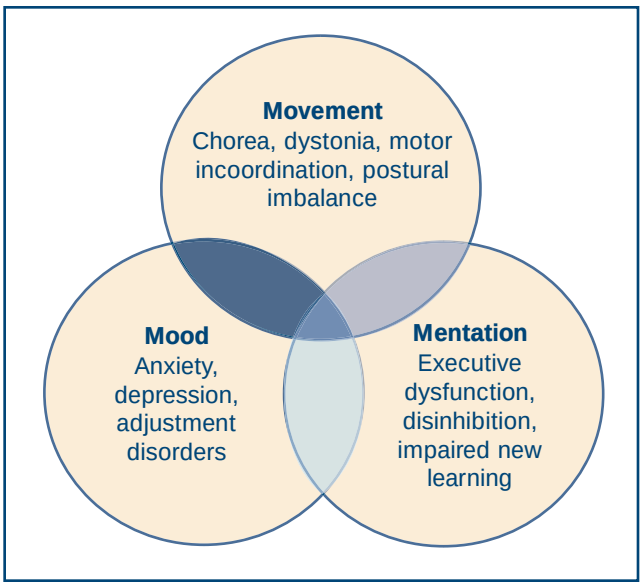

Figure 1. Triad of signs and symptoms characteristic of HD. There is a high degree of individual variability in extent of impairment in each area at different stages of disease.

With further research, Harry may find that some of his paternal cousins also have HD, underscoring the importance of generating a complete pedigree before considering the family history "negative."

As well, non-paternity is a factor in approximately 10% of cases with apparently negative family history for genetic disease.

Q *What tests would confirm a HD diagnosis ?*

A The gold standard is the gene test to determine the CAG repeat length of the two HD alleles. This test is highly sensitive and specific. Although computed tomography head scan had been routinely done to support a HD diagnosis, it is indicated only if other diagnoses are high on the dif-

ferential, such as neoplasm or other dementias.

Q How would you treat the movement disorder?

A Moderate to severe chorea that interferes with eating or drinking, results in injuries or contributes to weight loss and falls should be treated. Options include:

- low-dose haloperidol or risperidone (both can cause significant sedation and/or Parkinsonism);
- olanzapine, which may require doses anywhere from 2.5 mg/day to 30 mg/day to suppress chorea;[2] and
- tetrabenazine[3] (start with 12.5 mg/day, titrate up slowly and monitor frequently for new onset depression).

Mild chorea should not be treated, as it has little impact on the patient's level of function. There are no drugs on the market to improve motor coordination or postural balance in HD.

Finally, it is important to recognize that swallowing, as well as driving ability (due to diminished motor coordination and cognitive impairment), is often impaired early in HD. A swallowing study is useful for the former so strategies can be offered to lower the risk of aspiration. Patients should be counselled early in HD to take an annual road test to determine whether they remain safe drivers.

Q What are common psychiatric presentations of HD?

A Patients with HD can present with or experience a full range of Axis I psychiatric conditions, including anxiety (panic, phobias and obsessive-compulsive disorder), depression and, much less frequently, psychosis. These conditions are responsive to traditional pharmacotherapy.

Frequently, patients experience an adjustment disorder with mixed mood features in the immediate post-diagnosis period. This often responds to supportive measures and does not require pharmacologic intervention.

Other characteristic symptom complexes include frontal lobe symptoms (executive dysfunction, disinhibition and apathy), cognitive impairment and insomnia. In the earliest stages of HD (even before motor manifestations), it is common for patients to have difficulty with attention, new learning, organization/planning and shifting tasks, which can significantly impair ability to perform up to standard in their occupation.

The prevalence of HD is about 5/100,000; it's the most common inherited neuropsychiatric disorder.

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Q Do psychiatric manifestations require special treatment?

A Generally not. Depression responds to conventional therapy. Sensible "pharmacotailoring" (matching symptoms to drug profiles) may improve effectiveness.

The atypical antipsychotics, olanzapine and quetiapine, also appear to have beneficial roles in HD patients with anxiety, insomnia and psychosis. Quetiapine is less effective as an antichoreic medication due to its weak D2 binding properties.

Risperidone, a more potent D2 antagonist, is relatively more likely to cause Parkinsonism and this should be monitored carefully. Anticholinergics should be avoided whenever possible due to their propensity to cause cognitive impairment.

Q Is there anything to slow progression or delay HD onset?

A There are no drugs or nutritional supplements yet proven to slow progression or delay onset of HD. Several agents look promising based on preclinical studies in transgenic animal models. Some agents that have been studied and are undergoing further evaluation in human trials include:

- ethyl-eicosapentaenoic acid,
- creatine,
- Coenzyme Q10,
- minocycline and
- riluzole.[4-7]

Useful Web sites:

- www.huntington-study-group.org
- www.huntingtonproject.org

As well, in a collaboration between the Huntington Study Group and the National Institutes of Health, clinical and basic researchers are reaching a consensus on prioritizing agents for clinical trials. Dx

References

1. Brinkman RR, Mezei MM, Theilmann J, et al: The likelihood of being affected with Huntington disease by a particular age for a specific CAG size. Am J Hum Genet 1997; 60(5):1202-10.
2. Bonelli RM, Mahnert FA, Niederwieser G: Olanzapine for Huntington's disease: An open label study. Clin Neuropharmacol 2002; 25(5):263-5.
3. Ondo WG, Tintner R, Thomas M, et al: Tetrabenazine treatment for Huntington's disease-associated chorea. Clin Neuropharmacol 2002; 25(6):300-2.
4. Verbessem P, Lemiere J, Eijnde BO, et al: Creatine supplementation in Huntington's disease: A placebo-controlled pilot trial. Neurology 2003; 61(7):925-30.
5. Huntington Study Group: A randomized, placebo-controlled trial of Coenzyme Q10 and remacemide in Huntington's disease. Neurology 2001; 57(3):397-404.
6. Huntington Study Group: Minocycline safety and tolerability in Huntington disease. Neurology 2004; 63(3):547-9.
7. Huntington Study Group: Dosage effects of riluzole in Huntington's disease: A multicentre placebo-controlled study. Neurology 2003; 61(11):1551-6.