

Neuropsychiatry of Huntington's disease

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Psychiatric manifestations are an integral part of Huntington's disease. They may be divided into those syndromes which resemble idiopathic disorders, but for which HD patients may be particularly at risk, those constellations which are peculiar to HD and related conditions, such as the executive dysfunction syndrome, and those symptoms that can truly be regarded as nonspecific, such as delirium. Most of these problems are believed to arise from subcortical neuropathologic changes. Major depression is a common psychiatric diagnosis, but the executive dysfunction syndrome, a difficult-to-define condition characterized by often simultaneous apathy and disinhibition, may be even more widespread. There are no large controlled studies of psychiatric treatments in HD, but case series, anecdotal reports, and clinical experience indicate that many of these syndromes respond readily to treatment. Further study of the neuropsychiatry of HD may help to reveal the underpinnings of psychiatric conditions found in the general population.

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In attempting a treatment of the neuropsychiatry of Huntington's disease (HD), it is necessary to avoid the pitfalls which stem from our imperfect understanding of the condition. The first is a tendency toward excessive reductionism. Since we are unable to grasp its essence, Huntington's disease comes to be regarded as a catalogue of its motor, cognitive, and behavioral signs and symptoms. The striking chorea and dystonia are given primacy, and HD is thought of merely as a movement disorder, with the cognitive impairments and personality changes relegated to the status of accessory features. In fact, they are universal. Both may precede the emergence of involuntary movements,^{1,2} and any complete theory of Huntington's disease must explain all three. Likewise, rating scales and other instruments are useful in the assessment of psychiatric problems in HD, but not if they prevent us from moving from symptoms to syndromes. To speak only of "dysphoria" or "irritability" in HD, is to confuse the illness with the rating scale used to assess it, and puts one in mind of the comment attributed to Binet that "intelligence is what my test measures."

If over-reliance on rating scales and catalogues of symptoms constitutes an excessively Aristotelian approach, we must also avoid its Platonic opposite, which is to shoe-horn every psychiatric manifestation of HD into an existing idiopathic category, such as mania, or obsessive-compulsive disorder (OCD), as if each of these categories existed a priori, waiting to be unlocked by the HD mutation. We have almost no idea what causes these disorders

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in the otherwise healthy population, and thus possess no definitive means of diagnosis. Therefore, before we can say that we have identified “the same” conditions in HD, we must ask a series of questions. Does the HD-related condition have all the essential features of the idiopathic condition? Does it show a similar course over time? Is there evidence from imaging or laboratory studies that the conditions are related? Do they respond to the same treatments? Only by striking the right balance between these nominalist and realist extremes may we hope to understand and to devise effective treatment for the psychiatric manifestation of HD.

To reinforce this point, we will avoid the usual method of dividing the topic up by mental symptoms or by psychiatric diagnoses, and instead will organize our treatment into three heuristic categories: those psychiatric conditions found in persons with HD which strongly resemble idiopathic disorders found in the general population, such as Major Depression; those conditions found in HD which have no closely analogous conditions among the idiopathic disorder, and which appear to be either unique to HD or to the family of frontal-subcortical diseases, and injuries of the brain, such as the executive dysfunction syndrome, and those conditions, common in all patients with impaired brain function, which can properly be described as nonspecific, such as delirium.³

Overview of Huntington’s disease

HD is a hereditary neurodegenerative disorder caused by the abnormal expansion of a trinucleotide (CAG) repeat in the *huntingtin* gene of chromosome 4. The most common time of onset is in the fourth or fifth decade of life, but the first symptoms can appear anywhere from childhood to old age, with the age of onset inversely correlated with the size of the triplet repeat expansion. The progression of Huntington’s disease is inexorable, and usually leads to death within 15 to 20 years, with patients who are immobile and severely demented.

The movement disorder of HD includes both involuntary movements, such as chorea and dystonia, and impairments of voluntary movement, characterized by clumsiness, dysarthria, swallowing difficulties, falls, bradykinesia, and rigidity. Chorea generally predominates early, and is eclipsed by motor impairment as the disease becomes more advanced.

The dementia caused by HD is often described as a subcortical dementia, in contrast to a cortical process such

as Alzheimer’s disease (AD). This is a somewhat controversial distinction,⁴ but patients have relatively preserved memory yet experience more difficulty in executive function, impairment on tasks requiring attention and concentration, and erosion of personality.^{5,6}

Conditions found in persons with HD which strongly resemble idiopathic psychiatric disorders

Depression

A major depressive syndrome has been part of the nosology of HD from Dr Huntington’s first description of the disease.⁷ In fact, the lifetime prevalence is high, perhaps about 30% to 40%,^{8,9} with a suicide rate 4 to 6 times that of the general population.¹⁰ Severe cases may be accompanied by mood-congruent delusions or auditory hallucinations. Looked at subsyndromically, depressed mood is reported in approximately 35% to 60% of persons with HD, depending on the instrument used.^{11,12}

Other features of HD may lead to underdiagnosis or overdiagnosis of major depression. For example, common symptoms such as weight loss or apathy may be taken as evidence of a depressive syndrome, or, on the other hand, a classical major depression may be dismissed as the “understandable” reaction of the patient to having HD. Depression in HD is associated with reduced glucose metabolism in the orbitofrontal and inferior prefrontal regions.¹³ This finding is consistent with hypometabolism found in the prefrontal cortex of depressed patients without a primary neurologic disorder.¹⁴

It has been said that major depression can precede the movement disorder in HD, sometimes by years. While subtle psychiatric symptoms are more common in presymptomatic individuals,² there is little evidence to support this larger contention, and major depression is a common condition in the general population. The presence of depressive symptoms in an individual at risk for HD should not be used to make a diagnosis or serve as an indication for genetic testing.

The literature on the treatment of depression in HD by pharmacologic or psychosocial means is scant, but patients may respond to almost any standard class of medication¹⁵ and to electroconvulsive therapy,¹⁶ with the caveat that they will likely be more sensitive to adverse central nervous system (CNS) effects of treatment, such as delirium or agitation, than otherwise healthy individuals.

Mania

Mania and bipolar syndromes have a lifetime prevalence of 5% to 10% in HD,^{8,17} higher than would be predicted by chance. Patients may present with an elevated or irritable mood, impulsiveness, increased activity, hypersexuality, decreased need for sleep, and a grandiose self-attitude, and in severe cases may have delusions and hallucinations. As with major depression, mania can be the first indication of HD. Precision is required, however, in rendering a diagnosis of mania in HD, because personality changes such as disinhibition, irritability, and facetiousness which resemble mania are common in the disease. A classic presentation of mania would include three essential elements: an elevated or irritable mood, a grandiose (or paranoid) thought content, and symptoms of overactivity, such as racing thoughts, pressured speech, decreased need for sleep, or hypersexuality. This triad is frequently lacking in patients presenting primarily with "frontal" disinhibition.

The mainstay of treatment is a mood-stabilizing agent, usually an anticonvulsant such as divalproex sodium or a neuroleptic. Concern has been expressed about the use of lithium carbonate because of poor response and possible toxicity. Patients with HD are certainly more susceptible to dehydration and delirium, but responses may have been limited in the past because of imprecise diagnosis. The agent should at least be considered in cases with a classic presentation of mania.

Primary psychotic disorders

Delusions have been reported cross-sectionally in 11% of patients with HD and hallucinations in about 2%, using the neuropsychiatric inventory (NPI),^{11,18} or about 3% for each using an HD-specific instrument.¹² A 9% lifetime prevalence of schizophrenia has been reported in HD,⁹ but it is difficult to interpret such a statement, since we do not understand the causes of idiopathic schizophrenia, and even its core features are disputable. The most common psychotic presentation in HD appears to be poorly systematized paranoia and overvalued ideas that are commonly accompanied by aggression, irritability, and poor impulse control,¹⁵ and might better be thought of as part of the executive dysfunction syndrome of HD. Likewise, apathy and flattened affect can be found in schizophrenia, or in HD patients without psychotic symptoms. Isolated, well-defined delusional states and schizophrenia-like psychotic states are

uncommon, but, in our experience, have included erotomanic delusions, delusional parasitosis, delusions of bodily decay, and third-party auditory hallucinations. Psychotic symptoms in HD patients are usually treated with neuroleptics, but most practitioners have a preference for the atypical agents because of the lower risk of extrapyramidal side effects. Many patients respond to antipsychotic treatments, but some delusional states seem particularly incorrigible, consistent with the inflexibility manifested by many people with HD.

OCD

The rate of OCD is another controversial proposition in HD. Repetitive behaviors and speech, inflexibility, perseveration, and preoccupation with idiosyncratic topics are certainly common in Huntington's disease,¹² but these may be just another aspect of the spectrum of "frontal" symptoms that make up the executive dysfunction disorder. It has been reported that 22.3% of HD patients in a large study had obsessive or compulsive symptoms at their first visit,¹⁹ but the instrument used, the behavioral section of the Unified Huntington's Disease Rating Scale (UHDRS),²⁰ is poorly validated and lacks the rigor to distinguish true obsessions and compulsions from the personality changes commonly seen in HD. In a smaller study²¹ 50% of HD patients endorsed at least one obsessive or compulsive symptom on the Yale-Brown scale²² and symptoms correlated with deficiencies in executive functioning on cognitive testing. However, this scale was not designed to differentiate OCD from similar phenomena, and only the checklist questions and not the severity measures were administered.

Clearly, classical cases of OCD exist in Huntington's disease²³ and the frontal lobe, caudate, and globus pallidus have been implicated in OCD.²⁴ Estimates of the rate of OCD in HD and the degree to which certain dysexecutive symptoms should be given their own obsessive-compulsive category depend to a large extent on how much credence is given to the idea of an "obsessive-compulsive spectrum." Serotonergic agents such as selective serotonin reuptake inhibitors (SSRIs) and clomipromine are the mainstay of pharmacotherapy, but often behavioral management techniques, such as distraction and setting a routine, and managing the expectations of friends and family members through education, may be a more effective strategy. Cognitive deficits at this stage make cognitive therapies difficult.

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Psychiatric conditions specific to HD and other frontal-subcortical disorders

The executive dysfunction syndrome

Of all the psychiatric manifestations of HD, the executive dysfunction syndrome of HD, while difficult to define and characterize, may be the most common. Individuals with this syndrome may become apathetic, irritable, disinhibited, impulsive, obsessional, and perseverative. In a 134-person study, symptoms which might be termed “apathetic,” such as loss of energy and initiative, poor perseverance and quality of work, impaired judgment, poor self-care, and emotional blunting were the most common.¹² Factor analysis revealed an “apathy” factor, an “irritable” factor and a “depression” factor, and only the “apathy” factor correlated with disease duration. In another study,²⁵ the apathy factor, but not the other two, correlated with both motor and cognitive impairment. The implication is that those symptoms may be a more or less inherent part of HD.

Earlier treatments of the neuropsychiatry of HD tended to recognize that these seemingly disparate symptoms travel together, but simply lumped them all into a section called “aggression, irritability, and apathy,”²⁶ or referred to them as the “frontal lobe syndrome,”²⁷ in analogy to disorders with similar manifestations affecting primarily that part of the brain. In designing an inventory for the assessment and differentiation of frontal lobe dementia, Kertesz and colleagues designed the Frontal-Behavioral Inventory,²⁸ a 24-item questionnaire which divides symptoms into positive or disinhibited behaviors, such as perseveration, irritability, and jocularity, and negative or deficit behaviors, such as apathy, spontaneity, and indifference. This schema captures the seemingly paradoxical coexistence of apathy and disinhibition in the patient with HD. However, instead of the pseudoanatomical term “frontal,” we now prefer the more functional term “executive dysfunction syndrome.”³ Although they may be different sides of the same coin, we will deal with some of the major symptoms of the executive dysfunction syndrome separately, for the purpose of discussing treatment.

Apathy

Apathy is more distressing to friends and family than to the patient experiencing it. Sometimes the only neces-

sary intervention is to educate caregivers and help them to revise their expectations, by explaining that apathy is a predictable symptom of HD, and that it is not synonymous with depression. Anecdotal reports have been published of the successful treatment of apathy with amantadine, amphetamines, bromocriptine, bupropion, methylphenidate, and selegiline.²⁹ A nonsedating SSRI, such as fluoxetine, sertraline, or citalopram may also be considered.

Other authors have suggested reducing medications that might blunt emotion or slow cognitive processing, such as the neuroleptics.³⁰ Nonpharmacologic approaches include avoiding open-ended questions or tasks, providing cueing, maintaining a regular schedule, and increased environmental stimulation, such as involvement in a day program.

Irritability

The key to management of irritability and aggression is to place the behavior in context, so as to identify and avoid precipitants. There are no large, systematic studies of the efficacy of psychotropic medications in HD-related aggression and irritability. Nevertheless, antipsychotics, “mood stabilizers,” and antidepressants, particularly the SSRIs, are frequently prescribed.

Perseveration

Some perseverative or fixated patients can be distracted, or will extinguish if given enough time. Others are incorrigible. In these cases, the family should be encouraged to “pick their battles.” Confrontations should be saved for situations having to do with safety. This will be an easier point to get across if the family understands that these behaviors are due to the HD itself and that their loved one cannot “be reasonable.” Sometimes perseverative patients are treated with SSRIs for their presumptive “antiobsessive” effect. There is some theoretical basis for a dopamine-augmenting strategy in the treatment of executive dysfunction. A case has been reported of successful treatment with amantadine of an HD patient with an extreme syndrome characterized by perseveration, disinhibition, and severe aggression,³ as well as a case series showing positive results in psychiatric inpatients with executive dysfunction in the context of various forms of dementia.³¹

Nonspecific psychiatric conditions also found in HD

Delirium

Delirium is common in HD, and may result from volume depletion, poor nutrition, medical complications, metabolic disturbances such as urinary tract infections and pneumonias, and medication effects. Occult subdural hematomata from unwitnessed falls and head injuries are also a common and dangerous cause of delirium. The rule of thumb is that nothing changes rapidly in HD. A sudden change in behavior or decline in cognitive abilities should prompt an evaluation for delirium. The definitive treatment for delirium is to discover and correct the cause, but low-dose neuroleptics are probably the safest pharmacologic treatment for short-term management of an agitated delirium.

Demoralization

Despite the caveat against assuming a reactive explanation for all depressive symptoms in HD, patients with HD can and do become demoralized. This occurs particularly at times of loss, such as when a person with HD is forced to stop working, or give up driving. Patients who are also suffering from a dysexecutive syndrome may find it especially difficult to move on, and hospitalizations and suicide attempts have resulted from such losses. Other times, patients who are doing well may bring up suicide as an option for the future, "before things get too bad." The clinician should listen sympathetically to such statements, which reflect the patient's fear of impending helplessness, but should not overreact. Few HD patients actually kill themselves in such a premeditated way, perhaps because they tend to become increasingly unaware of their deficits as cognitive and executive function declines.³²

Sexual problems

The most common sexual disorders in HD, hypoactive sexual desire and inhibited orgasm, have been reported in 63% and 56% of men, and 75% and 42% of women.³³ At the other end of the spectrum, sexual aberrations, such as sexual assault, promiscuity, incest, indecent exposure, and voyeurism, have been described in HD, no doubt fueled by the disinhibition, perseveration, and impaired judgment which characterize the disorder. There have been no sys-

tematic studies of management of inappropriate sexual behaviors in HD. In severe cases, treatment with an antian-drogen agent, such as leuprolide acetate, may be appropriate.

Sleep problems

Patients with HD may have insomnia for a wide variety of reasons, including depression, lack of daytime stimulation, deterioration of the sleep-wake cycle, and involuntary movements. Although these movements in HD tend to fade during sleep, they may present an obstacle to falling asleep or to going back to sleep after a nighttime awakening. A formal sleep study can be useful for confirmation. In such cases, bedtime use of neuroleptics or other drugs to suppress chorea may solve the problem. Agents such as sedating antidepressants and low-potency neuroleptics may be used judiciously. Oftentimes, however, the act of keeping the person awake and active during the day, such as by enrolling them in a day program, is the most powerful intervention for sleep. Benzodiazepine and other sedative-hypnotics are almost always the wrong answer in HD. Apathetic patients with HD often sleep excessively or spend an inordinate amount of time in bed. This may be acceptable to the patient and family if it is understood as a feature of the disease. In cases where harm could result because the person is not coming to meals or practising good hygiene, judicious use of amphetamines may be appropriate.³⁴

Conclusion

We have attempted not to simply catalogue the psychiatric manifestations of HD, but to reorganize them, in a way that reflects evolving thought on the subject and a state-of-the-art understanding of the disease. Psychiatric issues in HD are so common that the clinician should expect to see them at every turn. Not only are they the aspect of HD most susceptible to treatment, but they are also one of the most exciting avenues for research. Each psychiatric syndrome in HD, such as major depression, or executive dysfunction, can be regarded as an "experiment of nature," the explication of which has a great deal to teach us, not only about Huntington's disease, but about psychiatry as a whole. □

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Neuropsiquiatría de la Enfermedad de Huntington

Las manifestaciones psiquiátricas constituyen una parte integral de la Enfermedad de Huntington (EH). Ellas pueden dividirse en aquellos síndromes que se asemejan a los trastornos idiopáticos, para los cuales los pacientes con EH pueden estar particularmente en riesgo, aquellas constelaciones que son características de la EH y condiciones relacionadas, tal como el síndrome de disfunción ejecutiva, y aquellos síntomas que pueden ser considerados verdaderamente como inespecíficos, como el delirium. Se cree que la mayoría de estos problemas surgen a partir de cambios neuropatológicos subcorticales. La depresión mayor es un diagnóstico psiquiátrico frecuente; sin embargo, el síndrome de disfunción ejecutiva, una condición difícil de definir que se caracteriza por la aparición a menudo simultánea de apatía y desinhibición, puede ser aun mucho más frecuente. No hay gran cantidad de estudios controlados de los tratamientos psiquiátricos en la EH, pero series de casos, reportes anecdóticos y la experiencia clínica indican que muchos de estos síndromes responden fácilmente al tratamiento. Nuevos estudios acerca de la neuropsiquiatría de la EH pueden ayudar a esclarecer las bases de las condiciones psiquiátricas encontradas en la población general.

Neuropsychiatrie de la maladie de Huntington

Les manifestations psychiatriques font partie intégrante de la maladie de Huntington (MH). Elles peuvent être divisées en syndromes ressemblant à des troubles idiopathiques, mais touchant particulièrement les patients atteints de MH, en cortèges de symptômes spécifiques à la MH et aux troubles qui s'y rapportent, comme le syndrome dysexécutif, et en symptômes non spécifiques comme le delirium. La plupart de ces problèmes semblent provenir de modifications neuropathologiques sous-corticales. La dépression majeure est un diagnostic psychiatrique courant, mais le syndrome dysexécutif, un trouble difficile à définir dominé par une désinhibition et une apathie souvent simultanées, pourrait être encore plus répandu. Il n'existe pas de grandes études contrôlées des traitements psychiatriques de la MH. Des séries de cas, quelques rapports anecdotiques et l'expérience clinique indiquent qu'un grand nombre de ces syndromes répondent facilement au traitement. La physiopathologie des maladies psychiatriques de la population générale pourrait être mieux comprise grâce à des études ultérieures sur la neuropsychiatrie de la MH.

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