ABSTRACT: Huntington's Disease (HD) is a progressive degenerative disorder of the central nervous system inherited as an autosomal dominant trait. Clinically, the disorder is characterized by choreoathetosis (with age of onset typically in the late thirties or early forties) and neuropsychiatric disturbance. The striatum is particularly vulnerable to the degenerative disease process, with selective loss of medium spiny neurons and decreased levels of associated neurotransmitters, including substance P, GABA, met-enkephalin and dynorphin. Although the underlying pathophysiology is unknown, recent theories concerning pathogenesis have involved mitochondrial abnormalities and excitotoxin-mediated damage. The gene for HD has recently been discovered and characterized as an unstable CAG trinucleotide repeat sequence on the short arm of chromosome 4 (now known as IT15). The direct test now available for the HD gene has facilitated disease diagnosis, particularly for those with unclear family history or chorea of uncertain origin; presymptomatic testing is also available. Management of affected individuals is unsatisfactory as only symptomatic control is available. However, as the effect of the genetic abnormality may soon be known, specific treatment of the disorder may become available in the near future.

RESUME: Maladie de Huntington: progres recents dans le diagnostic et le traitement. La maladie de Huntington (MH) est une maladie degenerative progressive du systeme nerveux central dont l’heredite est autosomale dominante. La maladie se caracterise au point de vue clinique par de la choreo-atheose et des troubles neuropsychiatriques, dont l’age de debut est habituellement dans la trentaine avancee ou au debut de la quarantaine. Le striatum est particulierement vulnérable au processus degeneratif: perte selective des neurones epineux de taille moyenne et niveaux abaisses de leurs neurotransmetteurs dont la substance P, le GABA, la met-enképhaline et la dynorphine. Bien que la pathophysiologie sous-jacente soit inconnue, des theories recentes sur la pathogenese de la maladie propose que des anomalies mitochondriales et des dommages excitotoxiques sont en cause. Le gene de la maladie de Huntington a ete decouvert recemment et l’anomalie responsable de la maladie a ete caracterise. Il s’agit d’une sequence repetitive instable de trinucleotides CAG localisee sur le bras court du chromosome 4 (nominee IT15). Le test direct, qui est maintenant disponible pour identifier le gene de la MH, a facilite le diagnostic de la maladie, surtout pour les patients dont l’histoire familiale est obscure ou dont l’etiologie de la choree est incertaine. Le test presymptomatique est egalement disponible. On ne peut offrir qu’un traitement symptomatique aux individus atteints, ce qui demeure insatisfaisant. Cependant, les consequences de l’anomalie genetique seront probablement connues bientot et un traitement specifique de la maladie pourrait etre disponible dans un avenir rapproche.
CLINICAL FEATURES

The average age of onset of HD, defined by the onset of the motor disorder, is typically in the late thirties and forties. However, the disease has been reported in children as young as four years of age, as well as individuals in their seventies. The age of onset will vary among families, with some showing a consistently older age of onset than others. However, it should be recognized that there can be a wide range of age of onset among individuals from the same family. Sex of the transmitting parent plays an important role: children of an affected father may have a younger age of onset than the children of an affected mother.

Chorea is the most characteristic feature of HD, and refers to brief, irregular, jerky movements which affect the face and limbs. Initially, these movements begin as a complaint of restlessness in the face and extremities, and at this stage, the chorea may be incorporated into purposeful movements. Slowly, the chorea becomes more florid, involving the limbs and body axis and interfering with simple tasks of coordination. Athetosis and dystonia may be superimposed on the chorea, particularly in advanced HD, lending the motor disorder a writhing quality. Many patients are unaware of the chorea, particularly in the early stages, and deny that they are affected. This lack of patient awareness is in contradistinction to other hyperkinesias such as tics or myoclonus.

Hypotonia, mild hyper-reflexia, buccolingual apraxia and difficulty with repetitive fine finger movements are commonly associated with chorea in the early stages. Gait may be affected, resulting in a wide-based staggering gait with impaired stride length, sometimes referred to as Huntington's ataxia. As the disorder progresses, individuals develop bradykinesia, rigidity, spasticity, and an upgoing plantar reflex. Other late abnormalities include dysarthria, dysphagia and urinary incontinence. Eventually, the chorea attenuates and bradykinesia or spasticity is prominent in the terminal stage. Eye movement abnormalities are frequently present, even in early stages. These include difficulty in initiating voluntary saccades, inability to suppress head movements or blinking during voluntary eye movements, and gaze fixation abnormalities. An inability to suppress saccades to external stimuli has also been noted.

Cachexia is almost always observed in HD, occurring even when a high calorie diet is maintained. This suggests an associated hypermetabolic state. Although the majority of patients present with neurological symptoms, psychiatric manifestations occur as the presenting symptom in up to one-third of patients, and can occasionally precede the onset of the motor disorder by as much as 10-15 years. After disease diagnosis (based on chorea onset), family members frequently report that for some years prior to diagnosis, the patient no longer seemed like himself, was easily irritable, suspicious and impulsive. Personality change, depression, anti-social behaviour and delusional thinking can occur resulting in initial misdiagnosis of a psychiatric disorder such as schizophrenia or manic-depressive illness. Sexual disorders, including hyper-sexuality, hypo-sexuality, exhibitionism and other sexual deviations have been reported. A very high suicide rate in HD has been noted, which may be the result of depression, but in some circumstances, may be a reflection of the patient's choice, particularly if he has previously witnessed the deterioration of other family members from HD.

Cognitive dysfunction is invariably present in HD, and includes linguistic impairments, memory deficits, visuospatial problems, frontal lobe syndrome and the erosion of cognitive performance prior to the onset of the motor disorder. General productive linguistic abilities are preserved in HD patients. However, subtle linguistic deficits do exist and include reductions in number of words produced, syntactic complexity and phrase length as well as decreased articulatory agility, word-finding difficulty and impairment in the comprehension and discrimination of prosody.

Memory testing in HD patients reveals a unique deficit: while recall memory is usually severely impaired, recognition memory for the same material (especially verbal material) can appear almost normal. Remote memory, whether of the recent or remote past, is uniformly poor. It has been suggested that the memory deficit in HD may be a problem of retrieval of previously stored information, rather than a problem of encoding of information.

HD patients demonstrate deficits in the processing of visuospatial information as demonstrated by lower performance IQ (PIQ) than verbal IQ (VIQ) on the WAIS-R, with impairments on such tests as Block Design, Object Assembly, Picture Arrangement and Picture Completion. Visuospatial impairments in HD patients have also been shown on the Mosaic Comparisons Test, the Rey-Osterriech Complex Figure and the Money Road Map.

There is a striking similarity in symptoms between patients with HD and those who have sustained frontal lobe damage: like the latter, HD patients demonstrate problems in the planning, organizing, and sequencing of information as well as in cognitive flexibility and the formation of alternate strategies. These impairments are reflected in the Wisconsin Card Sorting Test, the Stroop Test, and the Tower of Hanoi puzzle and in the demonstration of movement sequences (e.g., use a key, sip through a straw).

It has been suggested that cognitive and perceptual deficits may be present prior to the onset of the motor disorder. These findings remain somewhat controversial, with variable findings within the literature.

Although the age of onset in HD is typically in the late thirties or early forties, there are two important variants. Juvenile HD is defined by disease onset prior to the age of twenty years. These individuals differ quite markedly from HD patients with older age of onset, as chorea is usually minimal or even completely absent. Severe, rapid mental deterioration, bradykinesia and rigidity are the predominant features with spasticity, cerebellar ataxia, myoclonus and epilepsy occurring frequently. By comparison, when symptom onset occurs in the sixth or seventh decades, chorea is the most prominent symptom. In these cases, the disease may have a very slow progression, and cognitive impairment may be minimal.

IMAGING

Computerized axial tomography (CT) scanning can be useful in assessing striatal and cortical degeneration in HD. In the early stages of the disease, CT of the caudate is normal. With disease duration of five years or more, caudate atrophy is apparent, and disproportionately high in relation to cortical atrophy.
Magnetic resonance imaging (MRI) does not provide improved definition of the caudate nuclei, but is useful in excluding other pathologies such as ischemic caudate lesions, Hallervorden-Spatz disease or multiple sclerosis. MRI has also been useful in demonstrating that in patients with HD characterized by rigidity, there is an increased signal intensity in the striatum that is not present in hyperkinetic HD patients.48

Positron emission tomography (PET) scanning in HD using 18F-deoxyglucose as a tracer typically reveals hypometabolism of the striatum, regardless of disease severity. Caudate metabolism correlates with cognitive function while putamen metabolism correlates with the onset of the motor disorder.12, 49-51 In patients in the earliest stages of the disease, striatal hypometabolism found in PET scanning precedes tissue loss demonstrated through CT scanning, particularly in the caudate, with other areas demonstrating normal metabolism; later stage HD is also accompanied by cortical hypometabolism.52, 53 Caudate hypometabolism has been reported to precede motor abnormalities44 although likely only for a short period prior to the detection of clinical signs. Caudate nucleus hypometabolism should not be considered diagnostic for HD, as similar findings have been reported in other disorders such as neuroacanthocytosis and dentatorubropallidoluysian atrophy.55 [The findings of a previous paper56 describing a family with benign hereditary chorea with abnormal PET findings, most likely represent HD (M Hayden, personal communication).]

A recent study has suggested that benzodiazepine receptor density, using 11C-flumazenil as a tracer, may provide a more sensitive measure of the progression of CNS dysfunction in early HD patients than 18F-deoxyglucose. With the latter tracer, the caudate, putamen and thalamus were all hypometabolic, but with 11C-flumazenil, only the caudate demonstrated decreased receptor density.57

NEUROPATHOPHYSIOLOGY

The study of the gross neuropathology of HD began in the late nineteenth and early twentieth centuries, most notably by Meynert, Golgi and Alzheimer. The best known gross neuropathology studies are those recent ones of Vonsattel and his colleagues. Through systematic study of a large sample of HD postmortem brains, Vonsattel et al.58 were able to confirm and extend the observations of previous researchers, in finding that 1) the caudate undergoes greater degeneration than any other structure, and 2) the anteromedial aspects of the caudate are more affected than the lateral, posterior aspects. This study was also the first to establish a grading scale for progressive macroscopic degeneration in HD ranging from 0 (HD diagnosis, but no gross changes) through 4 (concave caudate/ventricular interface) .58 Apart from striatal involvement, degenerative changes have also been noted in the cortex, globus pallidus, subthalamic nucleus, substantia nigra, nucleus accumbens and cerebellum.56-61

There are a number of neuronal types in the mammalian striatum; these include 1) the medium spiny neurons (which are the vast majority of the striatal neuronal population and form striatal efferents; associated transmitters include substance P, GABA, dynorphin and met-enkephalin), 2) the medium aspiny neurons (contained entirely within the striatum, do not form efferents; associated co-localized transmitters are somatostatin, neuropeptide Y and the biochemical marker NADPH-diaphorase/NO synthase), and 3) the large aspiny neurons (again contained entirely within the striatum and associated with acetylcholine).62-66

A common observation emerging from many early HD pathological studies was that small neurons were much more vulnerable to the degenerative disease process than larger neurons. This observation has been supported by recent investigations: it is well known that medium spiny neurons (those neurons that form the output from the striatum to other parts of the brain) undergo degeneration in HD while the medium aspiny neurons are spared. The loss of medium spiny neurons has been detailed in reductions of levels of or decreased immunoreactivity of associated neurotransmitters, including substance P, GABA, dynorphin and met-enkephalin.67-73 Ellison et al.74 and Beal et al.75 have shown that reductions in GABA and glutamate levels correlate with pathological grade: reductions in GABA and glutamate are found in the caudate before other areas of the brain, and progressive transmitter reductions are associated with increasing pathological severity. In a comparison of choreic or rigid HD patients, Storey and Beal76 showed 1) a greater loss of GABA in the external division (GPe) than the internal division (GPi) of the globus pallidus as well as 2) increased GABA levels in the subthalamic nucleus and thalamus in choreic than rigid HD patients. Finally, preferential loss of striatal neurons projecting to the GPe and relative preservation of striatal neurons projecting to the GPi has been found in early and presymptomatic HD.77, 78

Similarly, the sparing of medium aspiny neurons in HD is reflected in preserved immunoreactivity as well as elevated (3-5 times) levels of somatostatin, neuropeptide Y and NADPHdi/NO synthase. This preservation is likely reflective of tissue shrinkage as well as neuronal sparing.79-81

With respect to the large aspiny neurons, cholineacetyltransferase (ChAT) levels are severely reduced in HD post-mortem brain, while staining for acetylcholinesterase (AChE) reveals preservation of cell bodies. This apparent discrepancy may be resolved on the basis of localization of each of these elements: AChE staining may be preserved due to its localization within cell bodies, while ChAT levels are reduced due to loss from axons and terminals.82, 83

Striatal dopamine levels (measured via tyrosine hydroxylase activity) are relatively preserved in HD tissue, likely a reflection of preservation of the dopaminergic projection from the substantia nigra to the striatum.84 Neuroanatomical and neurochemical studies of the cortex in HD have revealed loss of large pyramidal neurons but a preservation of local circuit neurons associated with GABA and neuropeptide Y.85

The etiology of HD is unknown, but recent theories concerning pathogenesis have involved excitatory amino acids such as glutamate. In the attempt to elucidate the etiology of HD, a number of animal models have been developed. Pathological and behavioural changes similar to HD can be caused by intrastriatal injection of such neurotoxins as quinolinic acid in rats and primates.86, 87 Because quinolinic acid is a potent agonist of the N-methyl-D-aspartate (NMDA) subtype of glutamatergic receptors, it has been suggested that the degenerative process in HD is the product of an excitatory neurotransin,88 possibly rendering neurons bearing NMDA receptors particularly vulnerable to early damage. Such studies have led to clinical trials with drugs,
such as lamotrigine (M Hayden, personal communication), which blocks the release of glutamate; in the case of HD, this mechanism would be directed towards reducing glutamate release from the corticostriatal projection. It has also recently been suggested that primary mitochondrial abnormalities in HD render neurons more vulnerable to excitotoxin-mediated damage.\(^9\) Along these lines, NMR spectroscopy has been used to demonstrate increased lactate levels in occipital cortex and striatum of symptomatic HD patients, suggestive of defective energy metabolism.\(^90\)

**GENETICS**

From its earliest descriptions, HD has been recognized as a hereditary disorder, transmitted in an autosomal dominant pattern of inheritance (children with an affected parent have a 50% chance of inheriting the disease, regardless of the sex of the affected parent or offspring). Penetrance is complete, indicating that all individuals who have inherited the gene will develop symptoms, excluding those patients who die at an early age.

The clarification of the genetics of HD has been an exciting area of development in the past decade. In 1983, Wexler, Gusella and their colleagues demonstrated a marker for the HD gene on the short arm of chromosome 4,\(^9,1\) a discovery which permitted predictive and prenatal testing for persons at risk.\(^92,93\) The development of the polymerase chain reaction (PCR) in the late 1980s facilitated the identification of the HD gene (now referred to as IT15), part of which is a triplet repeat (CAG) sequence located at the beginning of the transcribed portion of the gene.\(^94\) All individuals possess this repeat sequence; it is the number of triplet repeats that is significant. Normal individuals have 11-31 repeats while patients with HD have 38 or more repeats.\(^95\)

Prior to the discovery of the HD gene, it had been noted that the age of onset of HD was related to the sex of the affected parent (i.e., genetic imprinting); most juvenile onset patients were found to have inherited the disease from their father, but if the disease was inherited from the mother, patients were more likely to have an age of onset similar to previously affected family members.\(^6,8\) Since the discovery of the gene this observation has been explained: the earlier the age of onset, the greater the number of triplet repeats for a given patient. Juvenile onset HD typically demonstrates the greatest number of repeat sequences (upwards of 55 repeats) while late onset HD shows the fewest number (38-43 repeats).\(^96\) It has been noted that, independent of age of onset, there is no association between repeat length and clinical symptoms at presentation.\(^97\) Further studies have shown that transmission of the gene through sperm results in an expansion of the number of repeats.\(^98,99\)

The discovery of the HD gene has also permitted the identification of “sporadic” cases of HD. In some families, the number of triplet repeat sequences may be in the intermediate range (34-38) and increase with successive generations (particularly with paternal transmission), finally resulting in the HD phenotype; this may account for cases of HD, which in the past, may have appeared to be spontaneous mutations.\(^100\) The location and nature of the CAG repeat has been found to be identical in all families tested in a variety of populations.\(^101\)

It is significant that up to 1% of individuals with clinical symptoms of HD may have a negative test result.\(^95\) In some families, a different genetic mutation may be responsible for the disorder. In others, a different disease process may be involved. It has recently been demonstrated that the genetic defect in dentatorubralpallidoluysian atrophy (DRPLA), a disease which includes choreoathetosis and dementia in its clinical symptomatology, is an expanded CAG repeat on the short arm of chromosome 12.\(^101-103\)

The messenger RNA transcribed from the HD gene is found in all organs, although it may be present in higher levels in the brain. The translated protein has not been characterized but appears to be different from any recognizable protein to date; it has tentatively been called “huntingtin”.\(^98\) The relationship between the protein and the pathogenesis of HD remains to be determined.

**DIFFERENTIAL DIAGNOSIS**

In an individual with a clear family history of HD and an autosomal dominant pattern of inheritance, the diagnosis of HD may not be difficult, although consideration of other possible causes of dementia and chorea is important. In the older patient, neurodegenerative conditions such as Alzheimer’s Disease, olivopontocerebellar atrophy (OPCA) and multi-infarct dementia may mimic symptoms of HD. In younger patients, conditions such as Hallervorden-Spatz Disease and Wilson’s Disease may cause a choreiform movement disorder and/or bradykinesia in the early stages.

One of the most important categories in the differential diagnosis is that of drug-induced chorea. For example, tardive dyskinesia can cause diagnostic confusion, particularly in the situation where an individual at risk for HD is started on neuroleptics for psychiatric problems. Other commonly used drugs such as phenytoin, lithium and digoxin have been reported to cause chorea (see Table 1 for a complete list of causes of chorea).

Prior to the discovery of the HD gene in 1993, confirmation of a diagnosis of HD required intensive investigation of all causes of chorea. With the development of an accurate DNA test, patients with typical symptoms but absent family history should have this test performed before all others. If the nucleotide sequences are within the normal range, a full workup is then required, including a CT/MRI scan, EEG, nerve conduction studies and bloodwork including CBC, ESR and smear for acanthocytes, as well as thyroid function tests, electrolytes, calcium, serum copper and ceruloplasmin, ANA, liver function tests, CPK, creatinine, VDRL and HIV. Post-mortem neuropathological analyses of the brain remains extremely useful, since clinical false positives and negatives occur in up to 15% of cases\(^104\) (although this error margin should decrease with the availability of DNA testing).

**MANAGEMENT**

Although there is no definitive treatment for HD, medical therapy and psychosocial intervention through a multi-disciplinary approach will help both the affected individual and family members cope with the disease.

Medical therapy revolves around treating the movement disorder and psychiatric problems. With respect to chorea, neuroleptics are useful in suppressing abnormal movements;
there is no evidence that one particular drug is better than another. Traditionally, haloperidol has been the drug of choice. It has been shown that low doses (up to 10 mg/day) are as effective as higher doses, and cause fewer side effects. A more useful drug, particularly with milder chorea, may be tetrabenazine, a noradrenergic depleting agent. It has not been released for general use, but is available in most Movement Disorder Clinics. The most significant side effects are sedation and depression; the main advantage is that there is little risk for developing tardive dyskinesia.

Urinary incontinence, a frequent problem in advanced HD, may respond to oxybutinin, or low dose tricyclic antidepressants at bedtime. Incontinence pads can be used by the patient in later stages. In the case of incontinence, infection always needs to be ruled out.

Over 40% of patients with HD experience depression, particularly in the early stages of the disease. This may be either reactive depression or an intrinsic component of the disease, and usually will respond to tricyclic antidepressants. The selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine, sertraline, paroxetine) may prove useful, although no formal trials for HD patients are available. The risk of suicide is significant in HD patients and appropriate questions should be asked in all patients to determine suicidal intent. Psychiatric symptoms, such as anti-social behaviour, may require neuroleptics and psychiatric intervention.

Ongoing supportive psychotherapy is frequently necessary, not only for the affected individuals, but for all family members. It will allow the affected individual to deal with development of disability, loss of career and independence. As the disorder progresses, the patient may become increasingly irrational, irritable and forgetful. Caregivers experience increased stress in dealing with the patient and their increased demands. Marriage and family breakup are not uncommon. Counselling is sometimes necessary to allay the guilt that family members associate with placing a loved one in a nursing home.

Support services from social welfare and Home Care will aid the caregiver in keeping the patient at home as long as possible. Physiotherapy and occupational therapy will keep the patient mobile in a safe environment. Dieticians ensure that the patient receives appropriate high calorie nutrition. Speech therapy maintains communicative abilities and deals with problems of dysphagia. Feeding gastrostomy may become necessary in later stages. As the disorder progresses, institutional care is required. Legal aspects of care are also important to discuss with the patient and family (e.g., guardianship and trusteeship) so that the individual remains well cared for, both medically and financially.

Genetic counselling at a Medical Genetics Clinic should be arranged in all families with HD, as most at risk individuals feel that they benefit from this knowledge. Some may wish to consider options that would prevent passing on the disorder such as sterilization, in vitro fertilization or presymptomatic testing.

The Huntington Society of Canada, a lay support group, is very helpful in providing information and support to families affected by HD.

**PREDICTIVE TESTING**

The identification of the gene marker has permitted presymptomatic testing for persons at risk since 1987. Such a test inevitably raises ethical issues but a survey of at-risk individuals showed that the majority felt that presymptomatic testing should be available so that informed decisions concerning careers, retirement and childbearing could be made as young adults. One drawback of the previously available gene marker test (the indirect test) was that it could only be performed when DNA from a number of affected and unaffected family members was available. Undetected recombination events were a source of error, resulting in test accuracy of approximately 95%.

The introduction of presymptomatic testing in 1987 in Canada was guided by a National Research Protocol which involved several sessions of pre-test and post-test counselling to ensure that individuals understood the possible and varied ramifications of testing. In particular, counselling sessions were felt to be necessary to provide ongoing support as psychological problems could occur in individuals receiving either an increased or decreased risk result. Most individuals who have undergone testing have indicated that the counselling experience was a positive one, regardless of the outcome. Presymptomatic and prenatal testing became available in 1992 as a service in some major centres.

The identification of the HD gene has permitted a more accurate test for persons at risk (i.e., the direct test). Use of PCR technology means that the tests can be done quickly and accurately.
using the patient’s DNA and DNA from other relatives is no longer required. Individuals with chorea of unknown etiology or absent family history are also able to receive an accurate diagnosis regarding HD status. Pre- and post-test counselling is strongly recommended for all participants to allow the individual to make an informed decision and provide ongoing support. The long term outcome of this type of testing is unknown, and information is still being gathered under a research protocol in some Canadian centres.

Presymptomatic testing needs to be carried out only under rigid guidelines. First, it should only be performed at the request of the patient. Other family members, physicians, insurance companies and lawyers should not be permitted to request testing under any circumstances. Second, the test result should only be released to the patient. If the result is to be released to another party, written consent is required from the patient. Third, it is presently inappropriate to test children under the age of majority because this knowledge may have significant negative repercussions in raising the child. In fact, presymptomatic testing of minors is not available in Canada.

HD is a progressive neurodegenerative disease for which there is no cure. However, much can be done to help the patient medically and to provide ongoing support to the patient and family. The identification of the HD gene has provided the impetus for much new research and the hope that the isolation of the genetic defect, identification of the etiology and development of an effective treatment, will soon be realized.

REFERENCES


