Huntington's Disease: Pathogenesis, Diagnosis and Treatment

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This review of the clinical features of Huntington's disease incorporates recent developments in pathophysiology, preclinical diagnosis and treatment. Although the mechanism initiating and guiding the cell destruction in this illness is currently unknown, the excitatory neurotoxin and the energy metabolism models may provide a valuable direction for future research. Similarly, although the precise relation between the neuroanatomical damage in Huntington's disease and the functional disability is not clear, applications of recently developed neural connection models have implicated a number of important brain-behavior associations. Preclinical diagnostic procedures have evolved through successive iterations that have each contributed to increased reliability. New functional brain imaging techniques are sure to add to this promising domain in the future. Preclinical diagnosis has been stimulated by the recent isolation of the Huntington's gene which has also rekindled awareness of the importance of informed genetic counselling and the inherent ethical dilemmas in genetic testing. Treatment approaches to Huntington's disease have been confined to palliative care with secondary symptom management and psychotherapeutic support. Experimental therapeutic strategies for the illness itself have had a rather disappointing record to date. Further developments in NMDA antagonism and neural cell grafting may provide some hope for the future.

Key Words: Huntington's disease; Huntington's chorea; pathogenesis; diagnosis; treatment; neuropsychology; genetic testing; NMDA antagonism

INTRODUCTION

Huntington's disease, as first described by George Huntington in 1872, is a chronic progressive neurodegenerative disorder affecting movement, cognition and personality. It is genetically transmitted as an autosomal dominant trait with complete penetrance and thus has an equal likelihood of affecting males and females. The clinical syndrome has a prevalence of five to ten per 100,000 and the number of gene carriers has been estimated at 20 per 100,000 (Conneally 1984). Age of onset is typically between 35 and 40 years (Ridley et al 1991; Myrianthopoulos 1966) but there is sufficient variability to support a distinction between a juvenile variant with onset before age 20 and a late onset variant principally evident after the fourth decade of life (Bruyn

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1968; Myers et al 1983). Although the primary pathophysiological anomaly underlying this disease is unclear, neuropathological and neurochemical studies have provided a relatively consistent picture of neural degeneration emanating from the striatum outward and possibly involving cortical damage as the disease progresses.

Clinical characteristics

Huntington's disease is associated with both involuntary and voluntary movement disorder which progressively worsens over the course of the disease. Characteristic abnormal involuntary movements involve limb choreoathetosis, most conspicuous in the upper extremities and appearing as a random jerky movement or a slow and sinuous writhing. Also common are choreoathetotic movements in the oro-bucco-facial regions that progressively interfere with the voluntary control of vocalization, chewing and swallowing which may leave the patient mute and at high risk of choking (Darely et al 1975; Podoll et al 1988; Folstein 1989). More subtle, abnormal voluntary movements are also present and may include bradykinesia evident in slowed initiation and execution of poorly coordinated movements. The voluntary movement disorder is particularly apparent in disruptions of gait, reaching behavior and manual dexterity (Girotti et al 1988). Disruptions of voluntary eye movements are evident in diminished velocity on ocular pursuit and an occasional nystagmus (Leigh et al 1983).

Psychiatric disturbances are prevalent and may appear before the onset of significant motor impairment (Folstein 1983; Schoenfeld et al 1984; Webb and Trzepacz 1987). Affective disorders are the most prevalent of the psychiatric disorders in Huntington's disease, with rates of major depression documented as high as 50% (Heathfield 1967) and mania or hypomania as high as 12% (Peyser and Folstein 1990; Folstein et al 1983). The affective component is of particular concern in light of the risk of suicide associated with the disease which has been estimated as high as seven percent (Reed et al 1958). Psychiatric symptoms associated with the putative subcortical dementias such as apathy, irritability and impulse control problems (Cummings and Bensen 1988) have also been observed in Huntington's disease (Dewhurst et al 1969; Burns et al 1990; McHugh and Folstein 1975; Caine and Shoulson 1983). There may also be a relatively high rate of violent behavior and criminality (Dewhurst et al 1970), explosive disorder (Webb and Trzepacz 1987) and a schizophrenia-like psychosis (Garron 1973).

Cognitive deficits appear with the abnormal movements and show a progressive unremitting exacerbation. General intellectual abilities show a mild diffuse impairment within the first year of onset of overt motor signs, with a robust impairment in memory for new learning, visuoperceptual abilities and visuomotor functions (Butters et al 1978; Moses et al 1981). More subtle early impairment may be observed in sustained attention, problem solving and verbal fluency which, along with memory, visuoperception and visuomotor functions tend to show the most rapid deterioration over time relative to other abilities (Brandt et al 1984; Caine et al 1978; Mayeaux et al 1986; White et al 1992). Dysfunction of the vocal apparatus aside, expressive and receptive language abilities may remain relatively stable or show only minimal disruption over the first few years of the disease. Anomia and aphasia, for example, are rare in the early stages and there is generally a sparing of language functions including comprehension, vocabulary and general knowledge (Butters et al 1978; Podoll 1988). As the disease progresses, however, language abilities begin to decline and combine with a more severe exacerbation of the early impairments to produce a general intellectual state that will approach the range of mental retardation (Norton 1975; Butters et al 1978; Josiassen et al 1982; Brandt et al 1984).

Neuropathology

Neuropathological studies have revealed atrophy, loss of neurons and gliosis reliably in the basal ganglia and somewhat less consistently in adjacent structural regions and in the neocortex. Neural degeneration begins in and emanates from the striatum, with the earliest and most severe pathology in the mesial region of the tail of the caudate spreading in mesio-lateral and caudo-rostral gradients outward to subregions of the putamen and pallidum with subsequent and more moderate cell loss in the claustrum, subthalamic nuclei and hippocampus (Bruyn 1968; Vonsattel et al 1985; Dom 1976; Myers et al 1991). Damage outside of the basal ganglia is less consistently observed and the specific relevance of degeneration in other neural networks has thus remained more speculative (Vonsattel et al 1985). With this caveat in mind, however, cell loss, gliosis and atrophy have intermittently been documented in the brainstem, spinal cord and cerebellum (Bruyn 1968; Rodda 1981; McCaughey 1961) and in neocortical structures, particularly the frontal and occipital lobes (Hedreen et al 1991; Bruyn et al 1979; Tellez-Nagel et al 1973; Lange 1981; De La Monte et al 1988).

Although a specific link between a particular biochemical abnormality and the pathogenesis of Huntington's disease has yet to be found, neuropathological studies have underscored a role of the small- to medium-sized striatal spiny neurons that contain gammaamino butyric acid (GABA) (Ferrante et al 1991). GABA is a neurotransmitter with a postulated link to the inhibition of spontaneous involuntary movements (Perry et al 1973). Whereas the larger aspiny interneurons are unaffected in the early stages of Huntington's disease, the spiny neurons are severely diminished (Graybiel and Ragsdale 1983; Ferrante et al 1985). Also diminished are the concentrations of GABA and its synthesizing enzyme glutamic acid decarboxylase in the striatum, pallidum and substantia nigra (Perry et al 1973; Stahl and Swanson 1974) and in other basal ganglia and diencephalic

structures including the nucleus accumbens, the subthalamic nucleus and the ventrolateral thalamic nucleus (Spokes et al 1980).

Etiology and expression

The mechanism by which the selective cell destruction in Huntington's disease is initiated, guided and maintained is currently unclear. However, recent advances in molecular biology and in the modelling of specific neural networks have provided a promising framework for future research in this area. Perhaps most significant has been the demonstration that a local overactivity of excitatory amino acids could result in sustained depolarization producing selective neuron death that is similar to the selective damage evident in Huntington's disease (Coyle and Schwarcz 1976). This observation has focused attention on the hypothesis that an abberation in the metabolism of an endogenous compound may result in neurotoxic concentrations in Huntington's disease with similar consequences. Particularly noteworthy are the products and intermediaries of the kynurenine metabolic pathway including quinolinic acid, kynurenic acid and 3-hyrdoxykynurenine (Beal et al 1986; Connick et al 1989; Pearson and Reynolds 1992). Although very promising, the excitatory neurotoxin model has yet to provide an acceptable account of the delayed onset of Huntington's disease or the progressive deterioration within the neostriatum (DiFiglia 1990).

The delayed onset and progressive course of Huntington's disease have been addressed in a recently developed model in which neural degeneration is postulated to be secondary to a genetic predisposition which accelerates an age-related decline in energy metabolism (Simpson and Isacson 1993). Animal studies have revealed neurotoxic effects of the mitochondrial inhibitor 3-nitroproprionic acid (3-NP) that are selective for striatal structures while sparing other cortical structures (Hamilton and Gould 1987). Moreover, when considered with age-related declines in the efficiency of energy metabolism, the phenotypic expression of a genetic disposition to mitochondrial failure may not be evident until later in life – a postulate that has received support from the specificity of 3-NP neurotoxic effects to older rats (Bossi et al 1993). This area holds considerable promise, particularly in combination with an excitotoxin model as suggested by the potentiation of 3-NP neurotoxic effects by NMDA (Simpson and Isacson, 1993) and the reduction of these effects by pre-treatment with NMDA antagonists (Ludolph, Seelig, Ludolph, Sabri, Spencer 1992).

Whereas the excitatory neurotoxin and the mitochondrial dysfunction hypotheses have suggested mechanisms for local cell damage, a third model has offered a possible map for linking the neuroanatomical damage to functional consequences. A series of circuits has been postulated for the topographical relations between particular nuclei of the basal ganglia and cortical structures (Alexander et al 1986; Cote and Crutcher 1991). For example, a motor circuit has been proposed, linking cortical motor areas predominantly to the putamen though connections to the globus pallidum, substantia nigra and thalamic nuclei. Similar circuits have been proposed for connections between frontal cortex and the caudate, and for connections between the limbic circuit and the caudate. The specific topographical relations of the cortical structures involved in these circuits has provided a basis for relating the neuropathology of Huntington's disease to a downstream disconnection of particular circuits (Reiner et al 1988; Weinberger et al 1988; Hasselbalch et al 1992). The significance of this circuitry to Huntington's disease is underscored by the relative emergence of clinical pathology in relation to the progression of neural damage. Neural damage that proceeds from the caudate to the putamen may thus suggest an early manifestation of cognitive impairments and personality alterations relating to damage to the fronto-caudal and fronto-limbic circuits, whereas subsequent manifestation of movement disorders may coincide with progression to the motor-putamen circuit. Preliminary evidence has been provided for a clinical progression from cognitive and personality alterations to motor dysfunction. The relative absence of cortical involvement outside of the frontal and limbic regions in the early stages may also account for the sparing of gnostic and language functions until very late in the disease. Therefore, models of basal ganglia circuitry may stimulate the development of valuable hypotheses regarding the onset and course of clinical features. This circuitry may also provide an important theoretical basis for the similarities in cognitive and emotional changes evident in Huntington's disease and other putative subcortical dementia conditions including Parkinson's disease and progressive supranuclear palsy (Saint-Cyr 1988). Moreover, particular circuits may provide relatively specific mschanisms for pharmacotherapeutic effects, as for example in the role of substantia nigral circuitry in the efficacy of dopamine antagonism by haloperidol in the treatment of early Huntington's disease (Albin 1989).

Preclinical diagnosis

The pursuit of a preclinical diagnostic procedure has persistently assumed a critical level of importance to both genetic counselling and to pathogenetic research. Diagnostic procedures have typically been unable to detect the disease until after the prime childbearing years, which leaves those at risk with uncertainty as to whether or not they will pass the disease on to their children. In the absence of a preclinical diagnosis, the search for a pathogenetic mechanism for the disease is also hampered. Although emotional disturbance and cognitive impairment may be evident prior to the onset of overt movement disorder, these markers have not been particularly useful in the preclinical diagnosis of the disease. Subtle preclinical neuropsychological impairments, for example, have suggested cognitive changes prior to overt dis-

turbance of motor function (Jason et al 1988; Strauss and Brandt 1990; Diamond et al 1992) but the predictive utility of these procedures has yet to be supported. Emotional and personality alterations have also been noted prior to the other symptoms (Folstein et al 1983; Schoenfeld et al 1984; Webb and Trzepacz 1987) but the specificity of these observations has been challenged by the prevalence of such disorders in nongene carrying children of affected persons (Strauss and Brandt 1990; Diamond et al 1992).

Neuroimaging studies of cortical function have to date also proven to be of limited diagnostic value, though anomalies have been revealed with electroencephalography (Scott et al 1972), regional cerebral blood flow studies (Weinberger et al 1988) and computed tomography (Josiassen et al 1983). Early studies using positron emission tomography did not provide evidence of aberrant cortical glucose metabolism, even in patients with relatively advanced disease (Kuhl et al 1984; Young et al 1986), but a more recent study has documented cortical deficits with particular involvement of the frontal lobes (Martin et al 1992). Thus, although the preclinical diagnostic utility of PET anomalies in the cortex is currently undetermined, the potential utility of this technique has yet to undergo thorough investigation. Neuroimaging studies of subcortical structures, including computed axial tomography (CT) and magnetic resonance imaging (MRI), have effectively documented striatal atrophy in patients with clinical evidence of Huntington's disease (Oliva et al 1993) but have not detected striatal damage prior to the overt expression of cognitive and motor deficits (Grafton et al 1990). Positron emission tomography has been the one exception to the limited success of examining subcortical structures in preclinical diagnosis. Hypometabolism of glucose in the striatum may be detected with PET before there is evidence of structural damage on computed axial tomography (Hayden et al 1986), cognitive decline (Kuhl et al 1984) or any clinical signs of the disease (Grafton et al 1990). Magnetic resonance high-speed echo planar imaging, which has certain spatial and temporal resolution advantages to PET (Belliveau et al 1991), has as yet not been applied to the study of Huntington's disease but certainly holds considerable promise of efficacy in further research on preclinical testing.

Two remarkable discoveries within the past ten years have significantly altered the preclinical diagnostic possibilities in Huntington's disease. The discovery in 1983 of a linkage between Huntington's disease and a restriction fragment polymorphism on chromosome 4 provided a preclinical diagnostic marker with up to 98% accuracy (Gusella et al 1983; Magenis et al 1986; Tibbens et al 1992). Even more significant has been the 1993 discovery of the Huntington's mutation, an expansion of a trinucleotide repeat at a gene, IT-15 (interesting transcript 15), on chromosome 4 and its novel protein product, 'huntingtin' (The Huntington's Disease Collaborative Research Group (HDCRG) 1993). The expansion has proven to be very robust, as exemplified by its presence in every case among 114 affected patients, with a range of 36 to 82 trinucleotide repeats on expanded alleles compared to a range of six to 31 repeats on normal alleles (Stine et al 1993). Although the allele is unstable with occasional random contractions and expansions which could account for the rare expression of Huntington's disease in the absence of affected parents, the expansion tends to increase in successive generations and the longest segments of this trinucleotide repeat have been observed in patients with juvenile onset (HDCRG 1993) and in patients with paternal transmission (Stine et al 1993). Moreover, earlier age of onset has been associated with an increased number of repeats ($r = -0.65$), though the number of repeats has proven less effective in the prediction of age of onset, particularly when the number of repeats is less than 39 (Stine et al 1993).

Preclinical screening for the Huntington's disease has been available in clinical practice for approximately five years using the marker polymorphism. The method was restrictive and cumbersome in that it could only be used for patients with living relatives who were willing to undergo extensive screening procedures and who were heterozygous for the necessary polymorphism. With the isolation of IT-15, it will now be possible to provide preclinical, including prenatal, screening for the Huntington's disease gene without extensive genetic testing of suitable family members. In the five years since the original genetic testing procedure was introduced to clinical practice, clinicians and researchers have begun to approach the ethical, social and personal consequences of the disease. Genetic counselling programs are being developed and evaluated, with particular relevance to prenatal prediction (Ball and Harper 1992; Nance et al 1991).

For clinicians in the field, the prospect of a preclinical test has generated considerable excitement. This enthusiasm may not necessarily be shared by individuals who are at risk or who are affected with the disorder. Since testing became available, as few as 13% of individuals who are at risk have participated in predictive testing programs (Bloch et al 1989). Perhaps this is best captured in a comment by the president of the Huntington's Society of America who herself underwent testing for the Huntington's marker. She stated, "In the abstract, it is easy to think that you would want to know. When it is time to find out, the possibility of a positive test is frightening. How many of us would really choose to be told how we would die?" (Hayes 1992). Prenatal testing has its own set of complex ethical issues. Even if we had the luxury of setting aside the bipolarity of the right to chose debate, the availability of a prenatal test would still pose an intense personal challenge to the Huntington's patient making a decision about having children. Extended consideration of these issues are available in a number of publications that warrant consultation relating to ethics and testing (Thomas 1982; Harper 1992; Harper et al 1991; Ball and Harper 1992), genetic counselling (Martindale and Yale 1983) and recommendations for administering testing protocols (Nance et al 1991). Caution has been encouraged in the screening of

patients (Farrer 1986), particularly in light of a possible (White et al 1992) but not consistently observed (Wiggins et al 1992) increase in the risk of suicide after testing.

Treatment

There is currently no effective treatment available to stop the progression of Huntington's disease. The duration between onset and severe disability or death averages 17 years (Martin and Gusella 1986). Therapeutic intervention has been restricted to genetic counselling (pre- and post-diagnosis), symptom management and palliative care. Pharmacotherapeutics have some utility in the reduction of movement disorders and psychiatric symptoms. In particular, low dose dopamine antagonists such as haloperidol or fluphenazine have proven useful in the attenuation of chorea, irritability, hallucinations and delusions (Barr et al 1988; Caine and Shoulson 1983; White et al 1992). Bradykinesia may be somewhat attenuated by closely monitored administration of dopamine agonists such as levodopa/carbidopa or bromocryptine (White et al 1992). Tricyclic antidepressants or monoamine oxidase inhibitors have proven somewhat useful in the treatment of depression in Huntington's disease, though the pharmacogenic effects appear specific to somatic signs of depression, with relatively minimal effects on the ruminative components such as low self-esteem and hopelessness (Caine and Shoulson 1983). Sleep disorder, characterized by restlessness while asleep and daytime sleepiness may be treated with clonazepam, whereas associated anxiety disorders may respond to anxiolytics (White et al 1992).

A number of behavioral treatment strategies have been proposed to reduce some of the more disabling aspects of certain symptoms associated with Huntington's disease. Given the potentially lethal consequences of dysphagia, it has been suggested that meals be monitored and that patients be trained in safe and effective eating strategies (Folstein 1989). The disabling effects of the progressive speech impairment may be reduced by limiting the demands placed on the patient, particularly with respect to the speed and clarity of speech (Folstein 1989). Early intervention with speech therapy to provide alternative communication strategies may also be of benefit (Hayden 1981). Relaxation therapies and cognitive behavior therapies may be of value in the treatment of affective disturbances (White et al 1992). Family counselling may provide an invaluable therapeutic outlet for the distress that family members will have to endure throughout the relative's illness.

Although there are no pharmacotherapeutics currently available with efficacy in the direct treatment of Huntington's disease, a number of experimental therapies have been developed. Attempts to increase available GABA, including the use of the GABA-mimetic muscinol (Shoulson et al 1978), isoniazid (Perry et al 1979; Perry et al 1982), the GABA-transaminase inhibitor alphaacetylenic GABA (Tell et al 1981), and the GABA receptor agonist THIP (Foster et al 1983) have not been successful in reducing the deterioration. Also, although baclofen was successful in limiting excess glutamate in the striatum, it did not influence the course or expression of the disease (Shoulson et al 1989). A postulated role of somatostatin in the dysregulation of other neurotransmitters prompted a trial of the somatostatin antagonist cysteamine which also met with no success (Shults et al 1986). NMDA antagonists, which have been implicated in a diminishment of 3-NP neurotoxic effects (Ludolph, Seelig, Ludolph, Sabri, Spencer 1992), have been applied with some success in attempts to slow the progression of the disorder but their utility has been questioned by a detrimental side-effect profile with chronic administration which may include a loss of normal NMDA receptor-mediated synaptic plasticity that may permanently affect learning and memory (Choi 1988; Collingridge and Bliss 1987). However, further refinements in NMDA antagonism may yet produce an essential therapy.

Outside of the pharmacological domain, perhaps the most promising therapeutic avenue has involved fetal cell grafts. Preliminary studies of rodents with fetal cells transplanted from the striatum to a lesioned caudate nucleus have shown development of neostriatal neurons and possibly the formation of appropriate efferent and afferent connections (Di-Figlia et al 1988). Further, some of the movement deficits induced by excitotoxin lesion have been reversed by such grafts in rodents (Isacson et al 1986; Isacson et al 1984; Giordano et al 1990) and nonhuman primates (Hantraye et al 1992). These promising animal data have inspired a recent study in which four patients suffering from Huntington's disease underwent bilateral transplantation of embryonal striatal brain to the caudate (Sramka et al 1992). As yet, the post-operative results of these transplantations have not been published but this area clearly offers new avenues for research and development on potential treatments for Huntington's disease.

CONCLUSION

Since the first clinical description of Huntington's disease, both the clinical and neuropathological parameters have become increasingly defined and the responsible gene itself has been isolated. However, the etiology of the disease and its pathogenesis continue to be poorly understood and current treatment approaches have remained relatively primitive. Some hope for the future has been offered by a number of recent developments in Huntington's disease research. The energy metabolism model, particularly when combined with excitotoxicity hypotheses, may provide a mechanism for the age-related expression of selective cell death occurring in this disease. The current use of positron emission tomography and the future applications of functional magnetic resonance imaging will, without doubt, provide critical insights into the nature and expression of the degenerative process. This may well further clarify brain-behavior relations when considered

within models of basal ganglia circuitry and combined with improvements in the description of the course and manifestation of the clinical pathology. Although clinical trials have yet to support a safe and effective therapeutic agent, an increased understanding of the pathophysiology and molecular biology of the disorder may well offer new treatment avenues. For example, additional research directed towards a minimization of the side-effect profile of NMDA antagonists would be of value. Recent applications of cell transplantation technology to Huntington's disease may also provide some hope for the future.

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