Huntington's disease – An overview

Name of Disorder: Huntington's disease

Essay Title: Huntington's disease – An overview

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Content:

Huntington's disease (HD) is an inherited single-gene neurodegenerative disorder caused by expansion of a repeating section of DNA in the gene coding for the protein 'huntingtin'. The expanded repeat is a triplet of cytosine-adenosine-guanine, or CAG, which occurs normally in all healthy individuals. However, the protein product has a toxic effect when there are more than 39 triplet repeats. The disease process affects the central nervous system and invariably progresses to dementia and death approximately 15 years after diagnosis. Although there is considerable diversity in the presence of symptoms, it is generally characterised by a triad of symptoms comprising motor, cognitive and psychiatric disturbances, with typical onset in middle age. HD is estimated to affect approximately 1 in 10,000 individuals, with significant inter-regional and inter-racial variability. Individuals with an affected parent have a 50% chance of inheriting the genetic mutation, irrespective of sex. Although those at-risk of carrying the defective gene may undergo genetic testing to confirm its presence or absence, a clinical diagnosis is only obtained once motor symptoms reach a threshold level of severity via the Unified Huntington's Disease Rating Scale. The age at clinical onset can be estimated using a simple formula that can predict the likely timing of symptom onset based on current age and CAG repeat length, although there is emerging evidence to suggest that other genes are likely to modulate onset and progression.

HD pathology is primarily caused by selective and progressive degeneration of structures deep within the brain. This leads to altered communication between a number of structures, causing widespread disturbances in brain networks and consequently impairs movement abilities, thinking, memory, behaviour and mood. Research using sophisticated brain imaging technologies has established that structural changes can be observed up to 15-20 years before clinical diagnosis, during the so-called "premanifest" stage of the disease. With disease progression there becomes more widespread degeneration, including cortical thinning of brain tissue. Functional brain alterations, which are known to precede notable cell loss, and include changes in communication between brain regions (known as functional connectivity), are both degenerative and compensatory in nature. Such alterations are associated with motor and cognitive performance, and the variation in symptom profile across individuals has been related to the brain's capacity to compensate for such changes in cell function. Emerging research has suggested that brain imaging technologies that can assess brain *physiology*, such as electroencephalography (EEG) and brain stimulation techniques (such as transcranial magnetic stimulation, TMS), may be extremely useful methods to bridge the gap between the observed changes at the cellular level and symptom expression, yet their investigation in HD remains very limited. These physiological technologies are likely to complement and further extend the knowledge gained from existing MRI methods that are more commonly used to detect change in brain structure.

The cognitive profile of HD is characterised by deficits in attention, working memory, information processing, psychomotor speed, and executive function (including planning, problem solving and mental flexibility). Such impairments have been observed during the premanifest stages

of the disease and are often very debilitating and significantly impact on an individual's capacity to function day-to-day. Moreover, mood changes are also very common and are likely to arise from disturbances in brain networks responsible for emotional regulation, as well as secondary to coping with a life-changing disease and an uncertain future. The distinctive signs of HD that warrant a clinical diagnosis, however, are the involuntary movements (known as chorea) and poor co-ordination of voluntary movements (e.g., executing and initiating movement). Motor symptoms include disturbances in eye movements, walking, speech, swallowing and fine motor control (e.g., handwriting, dressing), and such symptoms have been associated with a decline in daily functioning and participation in activities such as working, driving and self-care. Surprisingly, however, there markedly less understanding of how brain changes contribute to how the clinical symptoms develop throughout the early and middle stages of HD and as the disease progresses towards death.

Despite the wealth of research to date, including the discovery of the HD gene in 1993, there is no cure, and only moderately effective drug remedies aimed at symptom amelioration are available. There is a current international focus to identify sensitive brain measures that can capture disease progression during both the premanifest and diagnosed stages of HD for use in future clinical trials. Given that changes in cell functioning precede cell death, it is expected that the application of therapeutic treatments will be able to delay the onset and/or slow the progression of the disease. Thus, it is hoped that future treatments may prolong the time-span of relative health in gene carriers and ultimately improve quality of life. As a single-gene disorder, with selective degeneration in particular brain regions, outcomes from HD research has wider applicability and impact on its potential to inform the assessment and treatment of other neurodegenerative and neurological conditions, including Parkinson's disease and Friedreich ataxia.

Some useful resources for further information:

CHDI Foundation, Inc (New York, USA): http://chdifoundation.org/

PREDICT-HD (University of Iowa, USA): https://www.predict-hd.net/

TRACK-HD (University College London, UK, HD Clinical Research): http://hdresearch.ucl.ac.uk/

IMAGE-HD (Monash University, Georgiou-Karistianis Experimental Neuropsychology Research Unit): http://www.med.monash.edu.au/psych/research/teams/enru/programs.html

Huntington's Victoria: http://www.huntingtonsvic.org.au/