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Abstract

Huntington's disease is a neurodegenerative disease that leads to gradual extensive brain damage, especially in the striatum and the cerebral cortex. Initial symptoms are cognitive difficulties, loss of motor control, and sudden mood imbalances. Cognitive function slowly declines into dementia, coupled with behavioral and psychiatric problems. Sufferers die within 20 years due to illness complications: a fall, pneumonia, or heart disease (Walker, 2007). This paper reviews the principle biological cause of the disease, its effect on the brain, diagnosis, and treatment.

Huntington's Disease

Huntington's disease is a severe neurological disorder that strikes about 1 person in 10,000 in the United States. It is also called Huntington's chorea, as in choreography, because sufferers' involuntary writhing sometimes resembles dancing. It causes widespread and pervasive damage throughout the brain, starting in the striatum and extending to many cortical areas. The most visible symptom is the lack of motor control, however, there are many cognitive and emotional deficits associated with the Huntington's: apathy, depression, irritability, psychosis, anxiety, obsessions and compulsions (Kingma, et al., 2007). The disease most often appears between the ages of 30-50, although it can occur in early childhood too. Huntington's is caused by a combination of known heredity factors and some unknown environmental factors. There is no cure yet for Huntington's disease. Currently, health care professionals treat the symptoms of the disorder with drugs; physical, occupational and speech therapy; and counseling.

Genetics

The gene that predicts Huntington's disease is autosomal dominant. (A recessive mutation leads to the loss of a desired function, while a dominant mutation creates an undesired function. The undesired gain here is the elongation of the Huntingtin protein.) The gene is shown in figure 1 and is located on the short arm of chromosome 4; It codes for the Huntingtin protein (Htt). In healthy individuals, the gene has a sequence of bases C-A-G (cytosine, adenine, guanine) repeated 11-24 times. Beyond normal threshold, the gene will code for a mutant elongated polyglutamine tract close to the N-terminus of the Huntingin protein (mHtt). Pathological indications begin when the gene has 35-38 repeats and predicts an elevated risk for late-onset of the disease, and/or of passing the elongated gene onto one's children. When the gene is passed on maternally, CAG tend to shorten; when passed paternally, CAG may elongate causing Huntington's to spontaneously appear in offspring, or decreasing the age of onset in offspring. The greater the number of C-A-G repeats, the earlier the onset of the disease and the more rapid the deterioration.

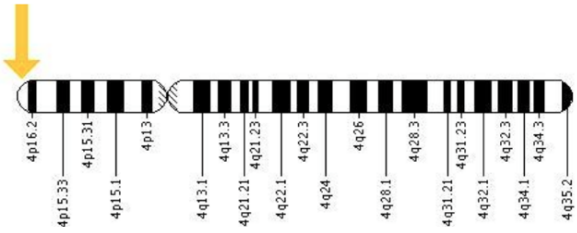

Figure 1: Chromosome 4 (U.S. National Library of Medicine, 2013)

Huntingtin Protein

The function of the Huntington protein is not entirely understood, but scientists have discerned that it plays a role in cell signaling, intracellular transport, and transcription. It is also crucial to neurological development of the fetus. The protein is found all over the body with the highest concentration in the brain and testes, and moderate amounts found in the liver, heart, and lungs (Walker, 2007).

Mutant Huntingtin Protein

Pathologically, abnormally long mutant Htt proteins break up into smaller, toxic segments that bind together and accumulate in the neuron. The inclusions present a mechanical blockage to neurotransmitters because the synaptic vesicles can no longer move through the cytoskeleton, as shown in figure 2. It is grossly detrimental in the striatum due to the presence of the striatal protein, Rhes (Subramananiam, et al., 2009). Rhes proteins induce sumolyation. Sumolyation [by Small Ubiquitin-like Modifier (or SUMO) proteins] is the modification of post-translational proteins that are involved in nuclear- cytosolic transport, transcriptional regulation, apoptosis, response to stress, and progression through the cell cycle (Hay, 2005). By this process, Rhes proteins prevent the aggregation of mHtt: this produces a soluble form of mHtt that is cytotoxic. Additionally, the cell's involvement in degrading the extra protein comes at the expense of other vital cell functions. Mutant Htt impinges on transcription regulation, apoptosis, tumor supression, mitochondrial function, and vesicle transport. Normally, when a neuron is recognized as a contributing, functional unit, it is nourished by

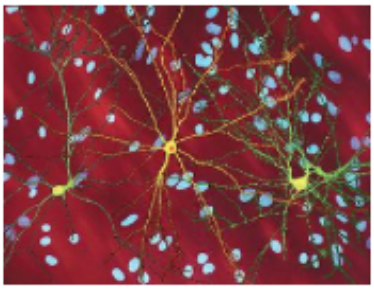

Figure 2: Medium spiny nueron (yellow) with nuclear inclusion (orange) (Huntington's Diesease 2013)

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nearby neruons and glial cells with brain-derived neurotrophic factor. However, due to mHtt interference, the neuron does not receive support and nourishment from nearby glial cells and neurons and the cell eventually dies (Walker, 2007).

Repercussion to the Brain

The Striatum

The striatum (figure 3) is the largest part of the basal ganglia, a sub cortical collection of nuclei. It is made up of two grey areas-the caudate nuclei and the putamen- and separated by the internal capsule. The internal capsule contains ascending and descending tracts between the cerebral cortex and medullary pyramids. This area is involved in modulating the afferent information from the cortex. Seventy-seven percent of the striatum is composed of medium spiny projection GABA-ergic neurons that receive converging stimulation from many areas of the cortex and feed selected signals to the prefrontal cortex. GABA is an inhibitory neurotransmitter and its release allows the activation of motor activity. Activation of this area correlates with expectations of rewards and consequences, and affects decision-making (Stocco, et al., 2010).

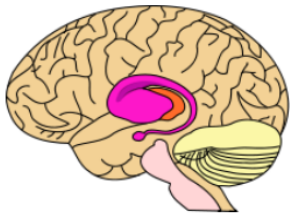

Figure 3 The striatum, colored magenta, is most damaged by Huntingon's (Huntington's disease, 2013)

The striatal medium spiny neurons of the basal ganglia are most vulnerable to Huntington's disease harm. Those that contain enkaphalin and project to the external globus pallidus are involved in circuits known as basal ganglia-thalamocortical circuits. The circuits project to the motor cortex and direct movement. For that reason, their damage predicts a lack of motor control (Walker, 2007).

Effect on Learning

The striatum also negotiates interactions between pairs of cortical areas. These associations create stimulus-response relationships that assist in learning skills and developing habit. There are several models that explain how this occurs. This paper describes the SPEED model. SPEED- Subcortical Pathways Enable Expertise Development- is designed to account for how automaticity is acquired (Ashbey, et al., 2007). The SPEED model asserts that the striatum mediates a conversation between a stimulus and a task-dependent motor response. When the correct response is achieved a burst of dopamine is released. Consequently, the cortex prefers the motor response associated with positive feedback, and in a mechanism known as Hebbian learning, the brain will strengthen the response tract and depress surrounding competing areas. These tracts are impaired in Huntington's patients and they are unable to learn new skills (Stocco, et. al., 2010).

Other Regions Effected by Huntington's

Other regions effected by the disease include the substantia nigra, cortical layers 3, 5, and 6, the Ca1 region of the hippocampus, the angular gyrus in the parietal lobe, the Purkinje cells of the cerebellum, the lateral tuberal nuclei of the hypothalamus, and the centromedial parafascicular complex of the thalamus (Walker, 2007).

The substantia nigra is part of the motor system. It receives stimulation from the motor cortex, premotor cortex, caudate nucleus and putamen. It sends information to the striatum and thalamus. It has a high dopamine level and is involved in planning and initiating movement, and reward.

The Ca1 region of the hippocampus is involved in long term potentiation for memory and learning and also indicated in mood regulation (Macey, et al., 2009) A dysphoric mood was associated with increase of hippocamal activity in Huntington's sufferers.

The angular gyrus in the parietal lobe is involved with number processing, spatial recognition, memory retreival, attention, theory of mind, and language. The angular gyrus has a substantial projection to the caudate nucleus and the diseased suffer considerable loss in this area (Macdonald, et al., 1997).

The Purkinje cells of the cerebellum, with an elaborate tree-like network of dendrites, are some of the largest cells. These cells play a crucial role in coordinating movement. HD is associated with reduced Purkinje cell density (Jeste, et al., 1984).

Results from post-mortum analysis of patient's with motor disturbances also display neuronal loss in the NTL (Lateral Tuberal Nucleus of the hypothalamus) (Kremer, et al., 1990). In humans, the NTL appears to control body weight and thermoregulation.

The centromedial (CM) and parafascicular complex (Pf) of the thalamus each contribute excitatory input to the striatum. The CM projects to the entire sensorimotor area of the striatum and the Pf provides complementary input to the associative region (Sadikot & Rymar, 2009). They also receive input from the motor and associative limbic system.

Diagnosis

Before being diagnosed, the patient may experience small imperceptable changes to personality, cognitive abilities, and motor control. Multi-tasking becomes difficult, the individual becomes irritable, forgetful, and unreliable, leading to anxiety. Diagnosis is usually sought once chorea and saccadic eye movement set in. Cognitive degeneration impairs planning, judgement, self-care, and organising and delays new-motor skill attainment. Mental degeneration is also significant; depression and suicidal ideation are common. Some patients also become manic and\or psychotic (Walker, 2007). A diagnosis is obtained by testing the patients ability to maintain a voluntary muscle contraction and fine motor execution. The patient may be

asked to stick out his or her tongue (HUNTINGTONS 3, 2009) or to carry out a finger-tapping rhythm.

Genetic Testing

Huntington's disease is a model for the opportunities and challenges of genome testing. Conclusive genetic testing is possible and can be helpful for people who want to be informed before they choose a career and start a family. However, fewer than 5% of those at risk seek testing. Individuals may want to avoid any discrimination associated with the diagnosis. Testing is also risky because it sometimes leads to suicide. Prenatal testing and preimplantation genetic testing are also optional, although many parents decline in the hope that by the time their children reach the age of risk there will already be a remedy in place (Walker, 2007).

Treatment

Medicine has yet to find a cure for Huntington's disease. Currently, patients can rest from the constant involuntary movements by taking antichoreic drugs like tetrabenezine or neuroleptics to control psychotic symptoms. Patients benefit from support groups, family support, and counseling. Physical, Occupational, and Speech therapy all help patients to maintain functioning for as long as possible (Walker, 2007).

Research

Research conducted along various avenues yield hopeful possibilities for the future. One potential therapy is RNA interference which aims to reduce the expression of the Huntingtin gene. The therapy was conducted on the Rhesus Macacque and established that a 45% reduction of the gene does not significantly affect motor function in healthy primates (McBride, et al., 2011).

Also in progress is research in cell therapy which aims to protect vulnerable neurons and replace dysfunctional cells through use of fetal or stem cells and through dispensing neurotrophic factors to support the brain (Clelland, et al., 2008).

Conclusion

Although HD's initial damage occurs almost exclusively in the striatum of the basal ganglia, much like a moldy strawberry that ruins the entire basket, in due course the spoil is far-reaching and extensive. The striatum is centrally located in the brain and projects widely. By associating with this defective spot, additional areas of the brain lose their functional capacity.

This paper is a detached, technical review of scientific review and research articles. Although it describes the clinical symptoms that HD presents, it hardly captures the heartache and distress the disease inflicts on the sufferers and their families. A diagnosis is a sure death sentence, prolonged and full of suffering. It is a twenty-year decline into certain doom- dementia and loss of motor function. It is humbling and difficult to confront an illness where sometimes the best one can do to help its victims is to validate their loss.

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