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HUNTINGTON'S DISEASE – A REVIEW

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Introduction

Huntington's disease consists of a genetic mutation which manifests itself in the form of loss of motor control and cognitive decline. In the present day, about 30,000 North Americans have Huntington's disease which is about 5 to 8 out of every 100,000. In general, the disease is less prevalent among African and Asian populations, especially when compared to European lineage. Huntington's disease is a dominant autosomal mutation, so if an individual has Huntington's disease, his or her children have a 50 percent chance to inherit the mutant gene, and if one copy of the mutated gene is present, the symptoms will appear [1]. Generally the time between the first manifestation of symptoms and death is about 20 years [2]. Currently, there is no cure for the disease.

History

In 1872 Huntington's disease was first identified and described in a paper by George Huntington [1], granting a model for the disease's phenotypes [3]. His patients had a common lineage – all had family members which had emigrated from Suffolk, England in the mid-1600s. Before him, his father and grandfather also studied the same group of patients [1]. It is believed the occurrence of Huntington's disease was seen in the 1600s, but was misunderstood as a “dancing disorder” and was viewed as witchcraft [4]. Although it is believed that previous characterizations of people with Huntington's disease were recorded, the credit for the development of the disease characterization is still granted to George Huntington [5].

Even after his paper was published, it was over 100 years before the gene associated with Huntington's disease was discovered [5]. In order to isolate this unknown gene, researchers used the DNA samples of families in Venezuela, where Huntington's disease and consanguinity are highly prevalent [5]. Finally in 1993, the researchers discovered a trinucleotide repeat which was

unstable when expanded [5] and which they believed was strongly linked to Huntington's disease.

Onset and Diagnosis

Onset usually occurs when the patient is in their 20s and 30s, but some cases have been seen in juvenile patients [1, 6]. Additionally, onset may come as late as 50 for other patients [3].

Generally, a person with Huntington's disease hardly, if at all, shows any symptoms before the middle of his/her life. Often, deficits in a person's development occur about 15 years before the onset of the disease; however, the deficit often goes unnoticed, until reflection after onset of more notable motor symptoms [5]. When more sensitive tests have been developed, these deficits will be more easily detected prior to significant decline [5].

Diagnosis of Huntington's disease generally occurs after the development of motor system problems [2], as well as language issues [7]. MRIs and other forms of neuroimaging are integral tool in diagnosing patients, verifying atrophy of areas of the brain due to the condition. Genetic testing may also be used to confirm the presence of the disease [8].

Pathology

Huntington's disease affects both cognitive and motor abilities. Patients experience chorea – over-the-top jerky movements that are uncontrolled. Due to these erotic movements, many see increased muscle tone, also called dystonia [5]. Often, the uncontrolled muscles begins with those farthest along the limbs from the trunk, i.e. fingers and toes, and those muscles in the face and tongue [8].

Memory, especially working memory, becomes severely limited. A loss of this type of memory is due to damage of the caudate nucleus and other subcortical areas. Nonetheless, damage to basal ganglia is reflected in the inability to follow procedural memory. Implicit

memories are also lost, culminating in difficulty chewing and swallowing. However, long-term memory is still available, and episodic memories, with prompting, can still be accessed [1].

Other brain functions are also affected by Huntington's disease. Cognitive speed, inability to concentrate, trouble processing problems to come to a solution, and spatial functioning are all impaired. It is harder for Huntington's disease patients to initiate behaviors, yet once started, they become fixated on these behaviors, losing sight of other activities [1]. As patients handle loss of control, tempers often become heightened and cause increased violence. Over time, they may unwillingly suffer from organic denial, not believing anything is wrong with them [1]. While those with Huntington's disease still understand the concept of emotions, they often cannot recognize how emotions look on the face, and therefore social relationships suffer [1].

About 40 percent of those with Huntington's disease also suffer from depression. This is a treatable aspect of Huntington's disease, yet it is often undertreated and under-recognized in the effects it may have on the patients. The population of those suffering from Huntington's disease have a 12-fold increase in the rate of suicide attempts compared to the population without the disease [1]. Suicide attempts are made by nearly 25 percent of patients [6].

Additionally, between 13 and 71 percent of those with Huntington's disease also suffer from anxiety [2]. Yet, if the patients are treated before the manifestation of symptoms, anxiety is usually only prevalent in 0 to 15 percent of patients [2]. One study showed that about 34 percent of Huntington's disease patients experience changes in their anxiety often [2]. No relationship seems to appear between anxiety and age nor gender [2]. A positive relationship is seen between anxiety and agitation, perhaps due to struggling relationships or because both begin to manifest as a result of the onset of disease and the many upcoming and ongoing changes [2].

Molecular Understandings

As of May, 2015, the complete molecular mutation of Huntington's disease and its effects were not understood [1]. The huntingtin gene (*htt*) is present on the short arm of chromosome four [1, 2]. Though not entirely confirmed, the huntingtin gene is believed to have a role in cell signaling as well as adenosine monophosphate as a binding protein and to help the body prevent cell toxicity and cell death [6]. The wildtype of the gene is generally seen in the nervous system [9]. The protein has a presence in the cytoplasm and vesicles of the neuronal cells of the brain [4].

This specific gene codes for three cytosine-adenine-guanine (CAG) cycles that are repeated up to 27 times in a normal, wildtype genome [1]. If an individual has between 36-40 repetitions, he/she has a chance of developing Huntington's disease, generally later in life but also may not [5]. The mutation that occurs in Huntington's disease involves this trinucleotide cycle continuing to repeat unchecked 40 or more times which forms the mutant huntingtin protein [1] found in exon one of the gene [4]. The repeat occurs on the 5' end of the chromosome and the repetitive sequence is then translated into a polyglutamine (polyQ) region [5].

Many relationships have been found in an effort to explain Huntington's disease. There is a negative relationship between length of the polyQ region and age of onset – earlier onset is linked to longer polyQ sequence. Since deterioration appears to occur exclusively decades into life, many believe that the real problem is not the presence of an enlarged polyQ region, rather a biochemical malfunction that occurs over time, yet this association has not been proven, and can be similarly seen in Parkinson's disease. Additionally, the environment and modifying genes can also have an effect on time of onset. A weaker correlation is seen between the polyQ length and how the disease progresses [5]. Using *C. elegans* as a model organism, age and length of polyQ

was shown to determine aggregation patterns of the polyQ region, which affects how the disease effects the motor functions of the animal [10]. Because of the aforementioned lag time in development of mental deficits and physical deterioration, one study proposed that the full phenotype is not fulfilled solely by genetic information; rather, modifiers act upon the polyQ region over time and spur on the degeneration to the full phenotype [3].

Dopamine, glutamate, and γ -aminobutyric acid are the main neurotransmitters affected by the disease [6]. The earliest areas affected by the brain are the striatum and sub-regions of the cortex [5] within the basal ganglia and cortex [6]. There is a severe loss of neurons in these areas [6]. However, the cerebellum is virtually left untouched. In the juvenile pathology, more widespread areas of the brain are affected [5].

In the protein interactions with mutated protein, cellular pathways are altered in such a way that increases neurons' susceptibility to various stressors [4]. Each cell in the body has the same amount of risk for cell death; however, it is the death of many cells over time that causes the symptoms to be seen [5]. There is significant evidence that astrocytes play a role in the development of Huntington's disease. More specifically, in several studies an increase of the mutant huntingtin gene was seen in astrocytes which leads to the onset of Huntington's disease symptoms as well as early death [11]. However, not enough research has been done to verify the relationship. With further study, therapeutic solutions may be developed that target astrocytes [11].

Very rarely does an individual have two mutated huntingtin genes, but in the few known cases, it seems that onset occurs in a similar time frame as those with only one mutated gene [5]. Most people suffering from the disease have both a wildtype and a mutant copy of the gene [4].

Deletion of the wildtype allele is lethal, which would indicate that the presence of a functioning wildtype allele is necessary to counterbalance the effects of the mutation to the point of keeping one alive [4].

Anticipation often occurs in the transmission of a mutant huntingtin gene, where the child has more CAG repeats than the parent. This phenomenon is generally exhibited if the father passes down the disease [1]. Usually, children whose fathers have Huntington's disease may see symptoms in themselves about eight years earlier than the father did [5].

Epigenetics

The focus of epigenetics is to explain the genotype-phenotype relationship beyond simply analyzing the DNA sequence. It has recently been suggested that stress of the nucleolus, the structure within the nucleus containing rRNA and rDNA necessary for ribosomal transcription, can evidence itself in the onset of Huntington's disease. Cajal bodies are accessory to the nucleolus and are linked to Huntington's disease and other diseases which contain elongated CAG sequences [4].

One paper, supported by the Korea Institute of Science and Technology, studied the nucleolar dysfunction that is present in Huntington's Disease and showed how the mutant huntingtin gene leads to alteration of the rDNA in a nucleolus, which causes lower levels of UBF1 and CBP, impairing the transcription of RNA within a cell. The implications of these decreased levels of CPB lowers the acetylation of neurons while increasing the methylation, therefore interfering with the functionality of neurons. Additionally, histone methyltransferases, which are epigenetic enzymes, are induced by the mutated huntingtin gene [4]. UBF1 is normally acetylated by CPB. When this does not occur the transcription cycle of RNA is severely hindered. In all of these epigenetic pathways, it is evident that the mutations present as a result

of the huntingtin mutation begin and continue a cascading event. More studies will likely be carried out based on the epigenetic implications found in this compilation of research [4].

Juvenile Disease

As previously mentioned, when the CAG repeating region is extremely long, Huntington's disease may occur in juveniles. If the polyQ region is greater than 50 or 60 glutamines, a juvenile form of the disease is experienced, with many different symptoms than the general disease symptoms [5, 7]. When Huntington's disease symptoms develop in a person before age 20, it is considered Juvenile Huntington's disease. If the person has not yet reached age 10, it is considered childhood-onset [7]. The youngest person to develop symptoms of Huntington's disease was two years old [5].

When Huntington wrote his paper about Huntington's disease, he did not report any cases with juvenile or childhood onset. However, in 1863, J.W. Lyon had already published a paper on what is now called Juvenile Huntington's disease, and soon after Huntington's report in 1872, A. Harbinson published the first report of childhood-onset of Huntington's disease [7], so it has been known about for many years.

Often, but not always, when a juvenile develops Huntington's disease, the father is the parent with the disease. During spermatogenesis, the CAG repeat length becomes less stable, so the length increases to the level which encourages the juvenile disease [7]. Juvenile patients often suffer from seizures and bradykinesia, a retardation of body movements [5], yet they usually do not develop chorea, and if so, is later in development [7]. The brain experiences deterioration in the cerebellum, hypothalamus, thalamus, frontal cortex, and hippocampus. Atrophy also occurs in the caudate and putamen of the basal ganglia [7]. Generally, Juvenile Huntington's disease has a three stage developmental model. It begins with behavioral

difficulties, followed by mental lapses, and ends in complete inability to function and generally increased seizures [7].

Therapies and Treatments

Currently, there is no cure for Huntington's disease; therefore physicians generally focus on treating the various symptoms associated with the disease [6]. In theory, knowing the gene and the mutation should allow for significant studies and development of treatments. However, since there are so few people with the disease, studies of treatments are difficult to conduct because researchers have trouble finding enough participants [9].

Pharmaceutical treatments and studies mainly address uncontrollable motor function. As of January 2014, tetrabenzene (TBZ) was the sole drug approved by the United States Food and Drug Administration to be used to treat Huntington's disease and the chorea that results. However, TBZ also has an effect on mood and ability to sleep, especially in the early stages of taking the drug. Other side effects like fatigue and dizziness arise. TBZ also increases the risk for suicide attempts, as it magnifies depression and suicidal feelings [6].

Dopamine and glutamate antagonists have also been used as treatment for chorea but are not as widely studied and tested. Some tried therapies attempt to target to reverse the dysfunctions in neurotransmitters glutamate, dopamine, and γ -aminobutyric acid but have not been largely successful [6].

Few studies have shown successful treatment of anxiety in Huntington's disease. Yet, some treatments seem to have a positive impact on Huntington's disease patients including olanzapine, psychological intervention, and an even longer multidisciplinary program. Even still, these studies were done focusing on many symptoms of Huntington's disease that also helped lower level of anxiety; they were not specifically treating anxiety in a Huntington's disease

patient [2]. Though some correlations have been made, some limitations and concerns in these studies are the inability to completely distinguish the definition of anxiety versus depression [2].

Some success has been seen in treating the failing motor systems through various chemical treatments. Though these do not offer full reversal of symptoms, it has been shown to improve the safety and quality of life of some recipients of treatment. Additionally, some patients find relief in antiparkinsonian medications [6]. Pharmaceutical treatment can also include managing various psychiatric symptoms also associated with Huntington's disease, including but not limited to depression, mania, and irritability. It is important to note that the treatment of Huntington's disease must be individualized to best help the patient – there is no one size fits all formula [6].

Future Plans

Many studies in the past have lead researchers to new ideas of ways to treat and hopefully cure Huntington's disease. In the near future, many of these will be tested for ability and safety in patients. PBT2 is a new compound being studied with this goal in mind. The drug would regulate the relationship between natural body metals and abnormal proteins, targeted based on the ability of the protein to cause atrophy in the brain [6].

Other compounds being studied as of January 2014 to treat Huntington's disease include coenzyme Q10, creatine, and polyphenon (2)-epigallocatechin-3-gallate, all of which have had some promising developments [6]. However, a trial with hopeful outcomes for coenzyme Q10 has since ended midtrial due to an unlikelihood that the treatment will work [9]. Even though clinical trials have thus far been unable to support these treatments, fish oil, coenzyme Q10, creatine, and the like are still used by some patients, due to their therapeutic abilities [9]. Delayed-release cysteamine (RP103) is also being extensively studied, but only 32 percent of

patients saw a retardation in the development of motor dysfunction, which is not a significant difference alone. However, after removing results of certain groups, this percentage increased, offering potential factors to further study in the future. Thus far, there is concern with RP103 increasing levels in liver function tests [9].

Studies are also interested in testing RNA interference, which could then genetically shorten any mutant huntingtin gene [6]. Additionally, repressing transcription with zinc finger proteins and translation of the gene with antisense oligonucleotides is being studied in hopes of silencing the gene [9].

True progress in the treatment of Huntington's disease will come once a preventative treatment is developed, one which will delay symptoms [6]. Even though thus far there has been no reversal of genetic mutation, it is possible to reverse the epigenetic changes that occur in the body. This knowledge lends itself to further studies of epigenetic therapies to help defend the nucleolus from changes from mutations [4].

Summary

First thoroughly characterized in the late 1800s, Huntington's disease now affects thousands of individuals in America. Huntington's disease has a late onset which severely affects motor and cognitive function. It is passed down from parent to child, and only one mutated gene is present when an individual develops the disease. Most symptoms are not able to be detected until midlife, though many mental and emotional deficits are present prior to physical onset. The progression of the disease lasts about 20 years. Jerky movements, irritability, depression, and motor decline are all symptoms to be expected when one is suffering from Huntington's disease.

Very rarely does one develop the juvenile onset of the disease, which consists of a longer CAG repeat sequence than the adult disease. When onset is earlier, the symptoms are much more severe, and death occurs much sooner.

Though there is no cure to date, there are some different treatments available to help aid in the severity of symptoms. Yet, there are promising research ideas which may lead to a concrete cure. With increased ideas and further understanding of the molecular level of the pathology, the previously unresolved “dancing disorder” may be closer to a cure than ever before.

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