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A Mini Review on Neurodegenerative Huntington Disease

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Abstract

The heterogeneous group of disorders characterized by the gradual degradation of the structure and function of the central nervous system or the peripheral nervous system are neurodegenerative diseases (NDs). Millions of people worldwide are affected by NDs, and the most common forms are Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). Huntington's disease is a rare, hereditary disease that causes nerve cells in the brain to slowly break down (degenerate). It has a broad effect on the mental ability of an individual and typically results in movement, perception (cognitive) and psychiatric disorders. It is caused by the HTT gene mutation and is inherited in an autosomal dominant way. Treatment is based on the symptoms that are present in each person and can involve different medications.

Keywords: Neurodegenerative diseases; Huntington's disease; Alzheimer's disease; Parkinson's disease

INTRODUCTION

Physician George Huntington recorded a family form of chorea in 1872, which his father and grandfather, both physicians, had previously noted on Long Island. His comments on the disorder now bearing his name, Huntington's Disease (HD), more than a century later, remain a straightforward summary of its major clinical features [1,2]. The disease "seems to obey certain fixed laws," he further noted. "It is "confined to a few families, usually attended by all the symptoms of common chorea, hardly ever manifesting itself until adult or middle life, and then gradually but surely coming on, gradually rising, and sometimes occupying years in its development, until the unfortunate sufferer is but a trembling wreck of his former self. Huntington observed that the "tendency to insanity" develops so that the "mind becomes more or less impaired, in many amounts to insanity, while in others, both mind and body gradually fail until death relieves them of their suffering." "For Huntington, the pattern of inheritance was also clear: "If one or both parents displayed manifestations... one or more of the offspring almost always suffer from the disease... but if these children go through a life without it by some chance, the thread is broken...." Finally, he noted the relentless, fatal course: "I never knew a recovery... at least it seems to be one of the incura. Huntington disease (HD) is a fatal neurodegenerative disorder that results in the first exon of the IT-15 gene encoding the Huntington protein from a CAG repeat expansion (>36) (HTT) [3]. Although the duration of the CAG-encoded polyQ tract appears to correlate directly with the severity of the disease and the tendency of HTT protein aggregation [4-6], it has been shown that other sequence features, including posttranslational modifications (PTMs), affect the aggregation, cellular properties and toxicity of HTT and can therefore contribute to HD pathogenesis [7-13].

Symptoms and the Affected Population

Huntington disease is a progressive brain condition that causes spontaneous gestures, emotional difficulties, and loss of thinking capacity (cognition). Huntington disease affects the whole brain, but certain areas are more vulnerable than others. The striatum is a deep area in the brain that plays a key role in movement, mood, and behavior control. The striatum is the part of the brain that is most affected by Huntington disease (Figure 1). The most common type of this condition, adult-onset Huntington disease, typically occurs in a person's thirties or forties. Irritability, depression, small repetitive gestures, poor balance, and difficulty learning new knowledge or making decisions may be early signs and symptoms. Many individuals with Huntington's disease develop gestures of repetitive jerking or twitching known as chorea. These movements are becoming more pronounced as the disease

advances. Affected people may have difficulties walking, speaking, and swallowing. People with this condition also experience personality changes and a deterioration in skills in thought and reasoning. Individuals with the adult-onset type of Huntington disease typically live around 15 to 20 years after signs and symptoms begin [14]. In infancy or adolescence, a less common type of Huntington disease known as the juvenile form starts. It also includes difficulties with movement and mental and emotional shifts. Slow movements, clumsiness, repeated stumbling, rigidity, slurred voice, and drooling include additional symptoms of the juvenile type. When thought and reasoning skills become impaired, school performance declines. Seizures occur in 30 percent to 50 percent of children with this disorder. Juvenile Huntington disease continues to develop quicker than the adult-onset form; people affected typically live 10 to 15 years after the appearance of signs and symptoms. An estimated 3 to 7 per 100,000 individuals of European descent are affected by Huntington's disease. In certain other populations, including people of Japanese, Chinese, and African descent, and the condition appears to be less common [15].

Causes and its Inheritance Pattern

Huntington's disease causes mutations in the HTT gene. The cytogenetic Location is 4p16.3, which is the short (p) arm of chromosome 4 at position 16.3 and the molecular Location is base pairs 3,074,681 to 3,243,960 on chromosome 4. The HTT gene provides instructions for the development of the Huntington protein. While this protein's function is unclear, it appears to play a significant role in the brain's nerve cells (neurons). A DNA segment known as a CAG trinucleotide repeat is implicated in the HTT mutation that triggers Huntington disease (Figure 2). This section consists of a series of three building blocks of DNA that occur several times in a row (cytosine, adenine, and guanine).

Normally, inside the gene, the CAG segment is replicated 10 to 35 times. The CAG section is replicated 36 to more than 120 times in individuals with Huntington disease. The signs and symptoms of Huntington's disease may or may not occur in people with 36 to 39 CAG repeats, while people with 40 or more repeats almost always develop the condition. An increase in the size of the CAG segment contributes to an abnormally long version of the huntington protein being formed. The elongated protein is split into smaller, toxic fragments that bind together and accumulate in neurons, thus interfering with the normal functions of these cells. The signs and symptoms of Huntington's disease underlie the dysfunction and subsequent death of neurons in some areas of the brain [16,17].

In an autosomal dominant pattern (Figure 3), this disease is hereditary, which means that one copy of the altered gene in each cell is enough to cause the disorder. Typically, an infected individual inherits from one affected parent the altered gene. In rare cases a person with Huntington's disease may not have a parent who has the condition. The size of the CAG trinucleotide repeat also increases in size as the altered HTT gene is transferred from one generation to the next. An earlier occurrence of signs and symptoms is commonly associated with a greater number of repeats.

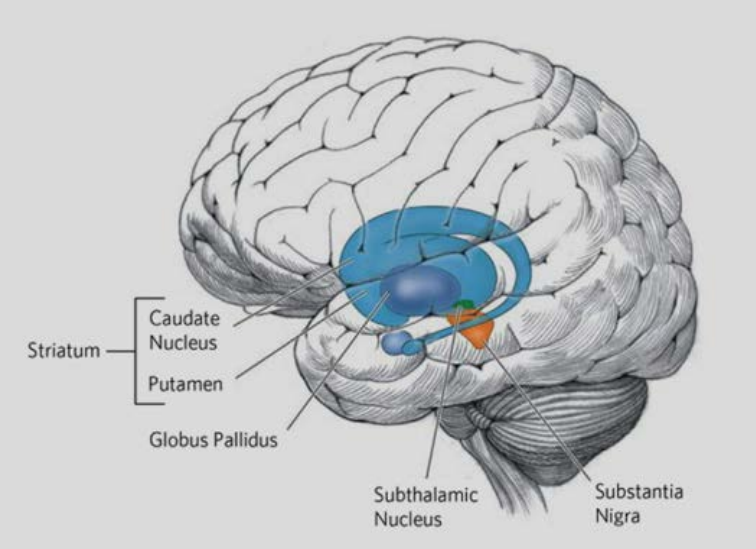

Figure 1: Showing striatum (part of the brain) which is most affected part.

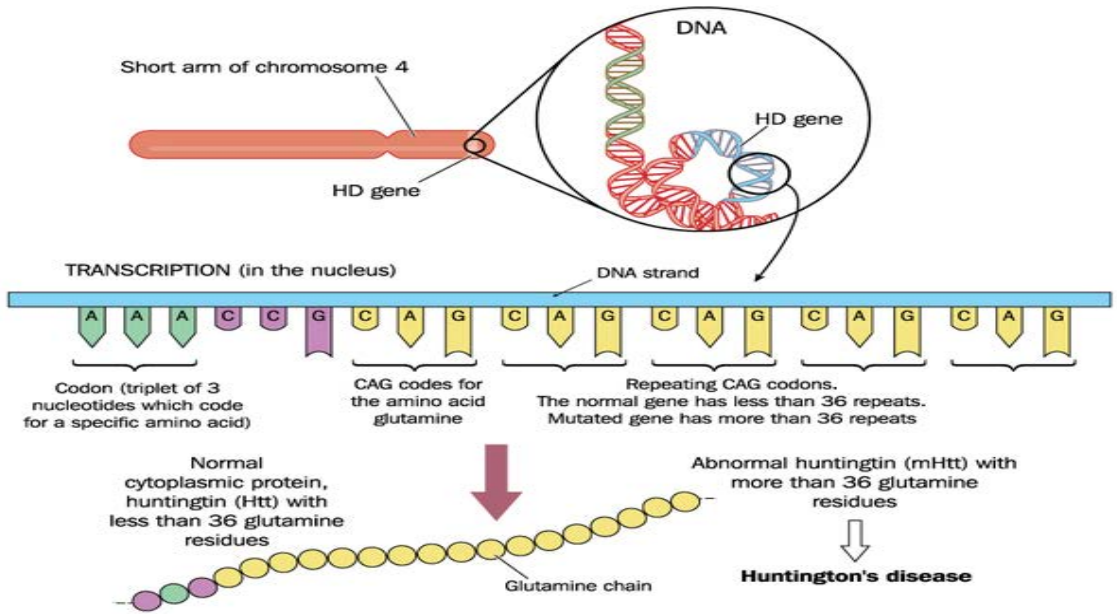

Figure 2: HTT mutation and repeat expansion mutation.

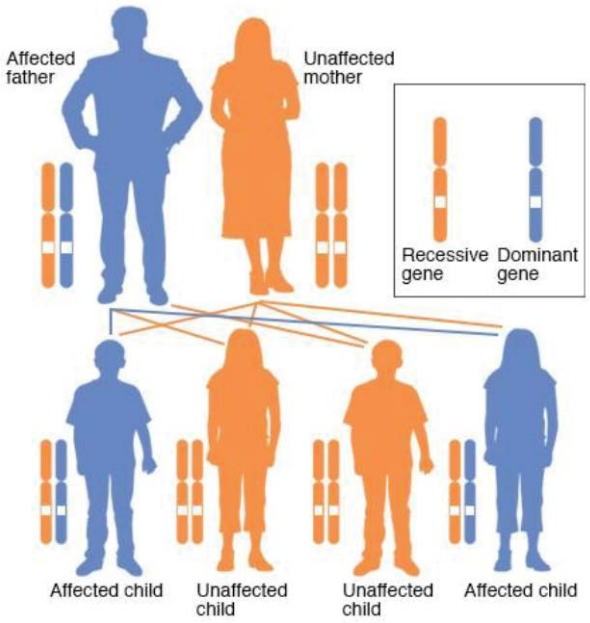

Figure 3: Autosomal dominant inheritance pattern

Anticipation is called this phenomenon. There are usually 40 to 50 CAG repeats in the HTT gene in people with the adult-onset form of Huntington's disease, whereas people with the juvenile form of the condition appear to have more than 60 CAG repeats. Individuals who have 27 to 35 repeats of CAG in the HTT gene do not develop Huntington's disease, but are at risk of having children who may develop the condition [18-21].

Diagnosis and Treatment

In individuals with characteristic signs and symptoms of the disorder and a family history consistent with autosomal dominant ancestry, a diagnosis of Huntington's disease is usually suspected. With genetic testing that detects an alteration (mutation) in the HTT gene, the diagnosis can then be confirmed [22]. The Genetic Testing Registry (GTR) contains information about the genetic tests for this disorder. Health care professionals and researchers are the target audience for the GTR. A health care provider or a genetics specialist should contact patients and customers who have specific concerns about a genetic test. The Neurogenetics Division at the University of Washington is a tertiary specialty which provides both general public clinical services and training to adults. They developed a booklet entitled, "Huntington Disease: Making an Informed Choice", which can be downloaded free of charge. Orphanet lists international laboratories for this condition offering diagnostic testing.

Sadly, there is no treatment for Huntington disease. The current aim of treatment is to slow down the progression of the disease and to help people affected work as safely and for as long as possible. The use of multiple drugs to treat symptoms such as irregular movements and behaviours is included in existing treatment plans. Among affected individuals, depression and suicide are more likely, so caregivers should watch for related symptoms and if possible, seek support. As symptoms of the illness intensify, more support, monitoring, and treatment are required for affected individuals [23].

CONCLUSION

Awareness of the progression of the disease has significantly improved since the discovery of the Huntington disease mutation over 20 years ago. After the disease starts, people with Huntington disease usually live for around 15 to 20 years. To help manage the symptoms of Huntington disease, drugs are available. But the physical, mental and behavioural deterioration associated with the disorder cannot be avoided by medications.

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