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Huntington's disease

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ABSTRACT

Huntington's disease is an autosomal, dominant, slowly progressive, inherited, incurable, and a neurodegenerative disease characterized by uncontrolled motor movements, cognitive impairment, behavior abnormalities which may finally lead to dementia. The main cause of this disease is the mutation in the huntingtin gene, which is an IT 15 gene. The Occurrence of this disease is more in western countries between the age group of 35 to 45. Symptoms of this disease depend upon CAG triplet repeat. Main symptoms are chorea, athetosis, jerks, weight loss, difficulty in speech are seen. Symptomatic treatment may improve the quality of the life of the individual or may decrease complications.

Keywords: Huntingtin gene (HTT), Cytosine adenosine guanine (CAG), Huntingtin protein, Tetrabenazine

INTRODUCTION

Huntington's disease is an autosomal, dominant, slowly progressive, inherited, incurable, and a neurodegenerative disease characterized by uncontrolled motor movements, cognitive impairment and behavior abnormalities which may finally lead to dementia. It is mainly caused due to the repeated number of cytosine adenine guanine (CAG) triplet in chromosome 4 in IT15 i.e., huntingtin(HTT) gene leading to the formation of mutant huntingtin gene (mHTT).

History

Previously this disease is called as Huntington's chorea, the name Huntington comes from a physician named George Huntington as he published the first description of the disease, that it is inherited and is characterized by excessive motor movements and neurophysiological deficits. In 1993, a consortium of researchers reported the successful discovery of an unstable triplet repeat expansion within the IT15 gene which is later on called as Huntingtin gene.

Huntingtin gene

Gene that causes Huntington disease is called as huntingtin gene, is an IT 15 gene. It is attached to chromosome4 which produces an important protein called huntingtin protein, which is needed by nerve cells in the brain and spinal cord for body development before birth. Although the exact function of huntingtin protein is unclear. HTT is expressed immune cells. Central and peripheral immune system abnormalities are seen in patients with Huntington's disease.

Epidemiology

The occurrence of Huntington's disease is more in western countries. In the US about 4.1 to 8.4 per 100,000 people are affected by Huntington disease. Huntington disease has majorly occurred in individuals of age between 35 to 45. Patients below 2 years and over 80 years are less affected. According to WHO the occurrence of HD in western countries is about 5 to 7 per 1000 individuals are between 35 to 45 years.

Clinical Manifestations

Symptoms of Huntington's disease depends on repeats of CAG triplet. Progressive CNS involvement including movement, cognitive, mood. According to Huntington Disease Society Of America, symptoms of Huntington's disease are closely related to Parkinson disease, Alzheimer disease and amyotrophic lateral sclerosis (ALS). It mostly occurs between 30 to 50 years, symptoms worsen after 10 to 20 years of occurrence. Movement problems majorly include chorea (purposeless or dance like), athetosis (slow movements), jerks weight loss difficulty in speaking are seen. Symptoms vary from one person to another person, even though they are of the same family. Stress and excitement may worsen the symptoms. Emotional symptoms may include aggression, anger, antisocial behavior, depression, excitement, lack of emotion, stubbornness. Three stages are included in HD they are early, middle, advanced stage. This classification is based upon the worsening of symptoms.

Early Stage

In early-stage small changes in coordination affecting balance is seen, slowing or stiffness, trouble thinking through problems is seen.

Middle Stage

In the middle stage dropping things that are due to unable to hold things is seen along with trouble in speaking and swallowing is seen.

Advanced Stage

During this stage complete dependence on others for their care is seen. Increase in clumsiness, trouble learning new information loss of memory, changes in speech is seen.

People without Huntington's have a variable number repeats of about 11 to 28. Persons having a larger number of repeats are more likely to develop the disease as penetrance is the repeat length dependent. It is ambiguous if the repeats are 29 to 39. The persons of about 29 to 35 repeats have not been found to develop disease among themselves, but they may pass to their children due to paternal meiotic instability. Reduced penetrance can be seen if the CAG repeats are 36 to 39. A penetrance is 100% if the CAG repeats are 40 or greater than 40 and are most likely to develop the disease.

Individuals who harbor/having two HD causing alleles will appear to develop symptoms about the same age as people with a single allele and same CAG expansion.

Juvenile Huntington's Disease

Juvenile Huntington disease is the rare cause. Juvenile onset contributes less than 10% of people with Huntington's disease. Juvenile Huntington's disease can be defined as the onset of symptoms before 20 years of age reflecting the earlier onset of disease. The paucity of movements, bradykinesia, an increase in the incidence of seizures is mainly associated with juvenile Huntington's disease.

In the disease course, cognitive impairment appears early often leading to dementia which profoundly impacts the quality of life.

Diagnosis

Identification of Huntington's disease and Alzheimer is some cases is complicated as recent studies detected the presence of neurofibrillary tangles in Huntington's disease which are commonly detected in Alzheimer disease. A physician will inquire the family history of the patient to confirm it as genetically inherited. Imaging tests like CT scan and MRI are done to determine changes in the patient's brain structure.

Recent studies evaluated the presence of huntingtin protein can be detected by simple saliva tests.

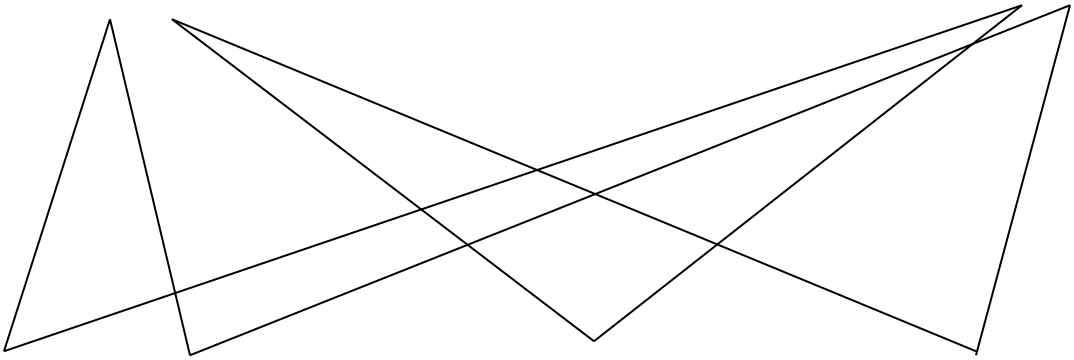
In Huntington's disease, unawareness of neuropsychiatric symptoms appears to be more common, but there is no clinical correlation to this is unclear. Few researchers examined that unawareness of neuropsychiatric symptoms are more common in early HD compared to premanifest HD. Diagnosis of neuropsychiatric symptoms can be made easy by identifying predictors of unawareness, executive impairment is much is a much useful early predictor of unawareness of neuropsychiatric symptoms in HD.

Causes of disease

A gene is a piece of biological information that is carried from parent to child. Huntington disease is caused if you inherited a faulty version of the Huntington gene. If an autosomal dominant has effected with disease 50% of chance is present in the occurrence of disease in a male or female child.

THE XY DETERMINATION IN HUNTINGTON DISEASE

XeXe X X Y



XeX XeY XeX XeY

XeXe = 100% Huntington effected male dominant gene. XY = unaffected female or recessive gene.
XeX = 50% chance of effected male child.
XeY = 50% chance of effected female child.

Genetic basis of Huntington disease defines disease as the expansion of CAG repeat encoding a polyglutamine tract in the N terminus of a protein product called huntingtin.

Pathophysiology

Neuropathologically Huntington's disease is characterized by the neuronal loss in the striatum and cortex at last. It also includes many other nuclei including the thalamus, hypothalamus, subthalamic nucleus, substantia nigra and cerebellum are also affected.

In cerebral cortex pyramidal neurons of layer 3, 4 and 6 ultimately degenerate. Symptoms of the later stage are due to the death of striatal neurons, whereas early symptoms are likely associated with cellular and synaptic dysfunction in the cortex.

Astrogliosis and selective neuronal loss in neostriatum are occurred by gross atrophy of caudate and putamen.

An early event in Huntington's disease is the alteration of transcription, intracellular signaling defects, alterations of synaptic function, defects in brain neurotrophic factor signaling. One hypothesis to explain the vulnerability of the striatum is that a group of factors that are selectively expressed in the striatum could markedly influence the survival of striatal cells expressing mutant Htt. For example, the presence of high levels of dopamine and D2 receptors in the striatum may have an important role in striatal vulnerability. Effect of Rhes on mutant Htt could underlie the selectivity of the degeneration that affects the striatum in HD, as Rhes has preferential expression in the striatum. Increase in plasma cytokine and chemokine levels

in patients correlate with disease progression and can be detected years before disease onset. Recent studies demonstrated that neurofilament light(NfL) in plasma shows a potential prognostic blood biomarker of disease onset and progression in Huntington disease.

Treatment

Huntington disease is an incurable and no specific treatment for this disease is not available currently, so specific symptomatic treatment may improve quality of life and prevent complications.

Tetrabenazine(xenazine) approved by FDA to treat jerky involuntary movements (or) chorea associated with Huntington disease. Lithium help with extreme mood swings and emotion.

For depression antidepressants like fluoxetine (Prozac, sarafem), sertraline (Zoloft), nortriptyline are used to treat.

Drugs to control hallucinations are clonazepam (klonopin), haloperidol, clozapine (clorazil). Risperidone which is an antipsychotic can also be used. Recently researchers reported in first human trail an experimental antisense drug (Ionis-HTTRx) successfully lowered the level of mutant huntingtin protein (mHTT) in spinal fluids of patients with Huntington's disease. Speech therapy, occupational therapy, and physical therapy are done to improve the quality of life.

CONCLUSION

After 140 years, even for today, many questions remained unclear about Huntington's disease regarding its pathology and its treatment.

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