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Letter to Editor

Huntington's Disease – Something More Than Saint Vitus's Dance

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Letter to Editor

Huntington's Disease (HD) is a neurodegenerative genetic disorder characterized by involuntary movements, cognitive impairment, and behavioural disturbances. The cause is a mutation in the HTT gene on chromosome 4, leading to abnormal development of the HTT protein and neurodegeneration. The disease typically affects individuals between the ages of 30 and 50. Juvenile HD refers to onset before age 20 and presents with learning and behavioural issues.

Etiology

The diagnosis of HD is made on the basis of symptoms and family history and is confirmed by DNA testing. The pathogenesis of HD involves abnormal HTT protein expression, which causes neuronal loss, particularly in the striatum. The length of CAG repeats in the HTT gene is a crucial factor in disease onset and progression, with longer repeats leading to earlier onset and more severe symptoms [1].

Epidemiology

Differences in HD case ascertainment and diagnostic criteria contribute to the varying prevalence rates worldwide [2]. HD is less prevalent in Asian populations than in European, North American, and Australian populations, possibly because of genetic factors.

Pathophysiology

HD is characterized by the degeneration of neurons in the putamen, caudate, and cerebral cortex [3].

Symptoms

Motor disturbances in HD typically begin in the distal extremities with involuntary movements that can progress to affect facial muscles. These symptoms gradually spread to the proximal and axial muscles and became more severe over time. Early symptoms often include hyperkinetic movements, whereas later stages are marked by hypokinesia, bradykinesia, and dystonia. Patients may present with dysarthria, dysphagia, and aspiration leading to pneumonia. Dystonia, tics and ataxia may also occur. As the disease progresses, individuals may have difficulty performing daily activities such as walking and standing, leading to an increased risk of falls. Behavioral and psychiatric symptoms of HD often appear early, even before motor symptoms appear. These symptoms often indicate frontal lobe dysfunction (frontostriatal degeneration), with features such as poor attention, depression, impulsivity, irritability, emotional blandness, apathy, and aggression. Cognitive decline is a significant symptom of HD, and often appears before motor disturbances, eventually leading to dementia. Unlike cortical dementia, memory loss in HD patients stems from an inefficient memory search rather than a lack of memory. Symptoms such as apraxia and aphasia, which are common in individuals with cortical dementia, are spared in HD. Secondary symptoms can include ataxia, gait abnormalities, eye movement abnormalities, and seizures in the juvenile variant.

Clinical Course

The clinical course and classification of HD can be divided into three stages [4]:

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1. Presymptomatic HD: Patients show no signs or symptoms but may exhibit changes in imaging.

2. Prodromal HD: Patients experience subtle motor and cognitive disturbances, as well as behavioral changes such as apathy and depression.

3. Manifest HD: Patients have prominent motor and cognitive disturbances that impact their quality of life.

Juvenile Huntington Disease

Juvenile HD usually begins before the age of 20, with more than 55 CAG repeats. It shares symptoms with adult HD but presents differently, often starting with behavioral and learning issues. Motor symptoms include hypokinesia, bradykinesia, and dystonia, with chorea appearing in the second decade. Severe mental decline, cerebellar symptoms, and delayed motor, speech, and language development are common [5].

Evaluation

The presence of motor symptoms, the absence of mental and psychiatric disorders, or often a combination of the three and a good family history, is usually sufficient to determine the disease. Laboratory tests are very useful in differentiating HD from other chronic HD-like diseases (acanthocytosis and McLeod syndrome). MRI is important for distinguishing HD from all forms of spinocerebellar ataxia and can be used to help distinguish HD in young adults from other metal accumulation disorders such as Wilson's disease and ceruloplasminemia [6].

Treatment/Management

No surgery is needed. A number of pharmacological and therapeutic interventions, including dopamine blockers, benzodiazepines, acetylcholinesterase, lithium, deep brain stimulation, and glutamate blockade agents, have been evaluated to prevent depression. Supportive care strategies as well as behavioural and psychological support may also be helpful and thoughtful. It is important to consider patient issues and psychological problems associated with HD, such as depression, anger, or violence.

The guidelines of the American Academy of Neurology recommend the use of tetrabenazine (TBZ), amantadine, or riluzole for the treatment of chorea.

For patients with the Westphal type (bradykinesia and rigidity), antiparkinsonian medications such as levodopa, dopamine agonists, and amantadine may be considered. Gene therapy offers exciting and promising advances in preventing HD. Silencing the mutated gene offers a therapeutic opportunity [7]. Drugs under investigation include those that inhibit apoptosis, excitotoxicity, HTT synthesis, HTT proteolysis and phosphorylation, and oxidative damage. Treatment options that have improved in animal models but have not yet entered clinical trials include: minocycline, memantine, sodium butyrate and phosphodiesterase 10a inhibitors. Investigational therapies including pridopidine, laquinimod, and the neutralizing antibody semaphorin-4D are still under development. Cell transplantation has shown good and safe results, and the effectiveness of mesenchymal stem cell injections is being tested.

Prognosis

HD is an incurable neurodegenerative condition lasting 15-20 years. CAG repeats can indicate when symptoms start and predict lifespan, with larger repeats leading to a faster decline in motor and cognitive function. Eventually, complete dependency leads to full-time care and death, most commonly from pneumonia or suicide.

Complications

Huntington's disease presents multiple complications, such as dystonia, swallowing difficulties, and chorea, with larger amplitudes leading to injury and fractures. Patients may experience a shorter lifespan because of these complications, with common causes of death being related to immobility.

Patient Education

Genetic counselling and predictive testing are available for asymptomatic adults at risk of HD. This enables informed decisions about care, finances, and reproduction, and allows participation in clinical trials. The determination of genetic risk before pregnancy is recommended. DNA banking for future use is also an option. Psychological support is important for dealing with the stress of living with HD.

Patients with HD often have an affected parent. A negative family history can result from not recognizing the disease, early parental death, an intermediate allele with reduced penetrance, or late-onset disease in the parent. The offspring of HD patients have a 50% chance of developing the disease [8].

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