ISSN: 0976-7126
Gupta *et al.*, 12(11):17-26, 2021

International Journal of Pharmacy & Life Sciences
Open Access to Researcher

Huntington's disease: Pathophysiology, Diagnosis, Treatment and Rehabilitation

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Article info

Received: 01/10/2021

Revised: 11/11/2021

Accepted: 24/11/2021

www.ijplsjournal.com

Abstract

This review of the clinical stage of Huntington's disease contain recent developments in pathophysiology, preclinical diagnosis and treatment. Huntington disease (HD) is a neurodegenerative disorder of the central nervous system characterized by undesirable involuntary movements, psychiatric and behavioral disturbances and dementia. Prevalence in the introvert population is estimated at 1/10,000-1/20,000. Mean age start of symptoms is 30-50 years. In some cases sign and symptoms will be start before the age of 20 years. with behavior disturbances and learning trouble at school (Juvenile Huntington's disease; JHD). The classic sign is chorea that involuntary movement to all muscles. All psychomotor processes become seriously slow down. The functional disorder is not clear, applications of recently developed neural connection models have suggest a number of important brain-behavior interrelation. HD is an chromosome dominant inherited disease caused by an expanded CAG repeat (36 repeats or more) on the short arm of chromosome 4p16.3 in the Huntingtine gene.

The longer the CAG repeat, the earlier the start of disease. Diagnosis is based on clinical symptoms and signs in a single or a parent with proven HD, and fixed by DNA resolution. Premanifest diagnosis should unique be performed by multifaceted teams in healthy at-risk adult individuals . they carry mutation or not. Differential diagnoses include other causes of chorea including general internal disorders or spontaneous disorders. hypomorphic (clinically diagnosed cases of HD without the genetic mutation) are observed. Prenatal diagnosis is possible by chorionic ileum sampling or ancients.

Key-words: Huntington's disease (HD), Epidemiology, Etiology

Introduction

Huntington disease

It is a chronic, progressive, hereditary disease of CNS in which degeneration of cerebral cortex and basal ganglia cause progressive chorea, Irregular involuntary movements and dementia. It also known as Huntington chorea, hereditary chorea or adult chorea. It was Ist described in 1872 by an American doctor, George Huntington[1].The hereditary nature of chorea was described in the 19th century by several doctors, but George Huntington's vivid description led to the eponymous designation of the disorder as Huntington's disease [2]. Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by motor abnormalities, psychiatric symptoms and cognitive dysfunction, [3]. Sign and symptoms of Huntington's disease consists of motor, behaviour and psychiatric disturbance. the first time, premanifest diagnoses could be made and as more diseases involving trinucleotide reproduction of CAG were found, CAG [cytosine (C), adenine (A), and guanine (G)], is a trinucleotide, the building stone of DNA.[4]

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In the brain, the basal ganglia is highly affected which involuntary muscle movements of the body or motor movement. The disease is characterized by a primary progressive loss of medium spiny estimate neurons within the basal ganglia .[5] It is a neurodegenerative disorder passing within families from generation to generation with onset in middle age and characterized by undesirable choreatic movements, behavioral and psychiatric disturbances and dementia [6].HD prepared as a model for many studies in medicine. Finding the gene opened new research lines, new models and for the first time a real story on the way to treat this destructive disease. Many symptomatic treatments are now available, but there is a need for better, modifying drugs [7]. Drug treatment is therefore analyze and based on expert opinion and daily practice. Although any signs and symptoms can be treated, it is not always fundamental to do so. The patient limitation in daily life determines whether the drugs are required or not [8].

Clinical Stages of HD :

HD diagnosed stage 1 (0 to 8 years since motor diagnosis): Maintains only marginal engagement in occupation having part time voluntary for salaried employment potential and maintains typical pre-disease levels of ability in all other basic functions such as financial management family responsibilities and activities of daily life (dressing, eating, bathing etc.) or satisfactorily in typical professional employment (perhaps at a lower level) and requires slight assistance in only you basic functions that is domestic chores, finances, or activities of daily life.

HD diagnosed stage II (3-13 years since motor diagnosis): Typically not able to work, requiring only scanty assistance in all basic functions: domestic, Finance, daily activities; or not able to work and exacting different levels of assistance with basic functions (some are still handled independently).

HD diagnosed stage III (5-6 years since motor diagnosis): unable to engage in employment and requires major assistance in basic functions: domestic responsibilities, financial affairs, and activities of daily living.

HD diagnosed stage IV (9-21 years since motor diagnosis): Requires major assistance in domestic responsibilities, financial affairs, and most of the activities of daily living. For example, awareness of the nature and purpose of procedures may be perfect, but a major assistance is required to act on them. Care may be provided at home but needs may be better provided at an spread out care facility.

HD diagnosed stage V (11-26 years since motor diagnosis): Requires major assistance in domestic responsibilities, financial affairs, and all activities of daily living. Full time experienced nursing care is required [9].

Epidemiology

Huntington's disease is a rare neuropsychiatric disorder with a prevalence of 5-10 per 100,000 in the Caucasian population. In Japan, a much lower prevalence of about one-tenth of prevalence of the Caucasion population is described Recently, several phenocopies have been described, all of which have an even lower prevalence (see paragraph on differential diagnosis) [10].

Etiology :

Huntington's disease is an autosomal mostly inherited disease caused by an prolonged CAG repeat on the short arm of chromosome 4p16.3 in the Huntingtin gene This gene codes for the huntingtin protein and, on axon 1, enclose the CAG tract. The wild-type enclose a CAG repeat, coding for a polyglutamine develop in the protein at that site in the range 6 to 26 [11].

Huntington's disease is couple with 36 repeats or more. Definite clinical symptoms will occur if the number of repeats have it all over 40. The range 36-39 leads to an incomplete penitance of the disease or to a very late access. The range between 29 and 35, the so-called intermediate allies, is unstable, which means that these allies are horizontal to changes during reproduction. Copying the gene may lead to mistakes and very usually leads to prolongation and a few times to shortening. This phenomenon is mainly observe in the male line of reproduction.[12]

The longer the CAG repeat, the earlier the access. When the disease starts before the age of 20 years,

ISSN: 0976-7126
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so-called juvenile Huntington's disease (JHD), the repeat often exceeds 55.[13] The length of the repeat determines about 70% of the change in age at access and gives no sign at all about the initial symptom. The only correlation now described is the faster weight loss associated with a longer CAG repeat. [14] Anticipation phenomenon is seen in Huntington families in the paternal line of inheritance.

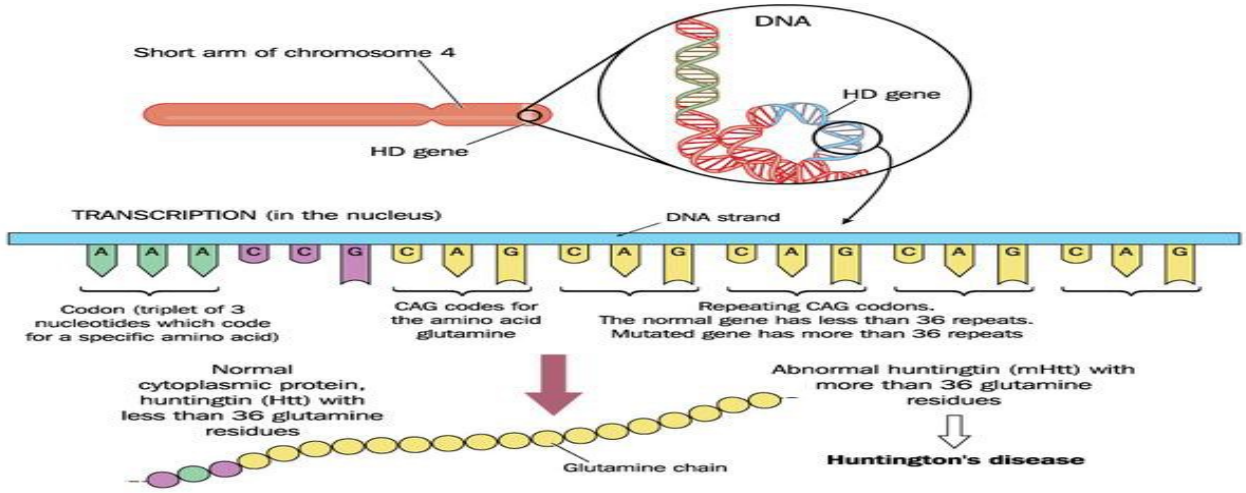

Figure 1: Genetics of Huntington Disease

The normal wild-type Huntingtin protein plays a role in synthetic function, is basic in the post-embryonic period, possibly has an anti-apostolic function and is possibly protective against the toxic mutant, huntingtin.[15] There is evidence that the mutant form leads to a gain of function as well as to a loss of function. The role of the mutation has been studied in many models: cells, C. Elegans, fibroblasts, drosophila, rat, mice, sheep and monkey. Mice models are most commonly used. As neuronal intranuclear and intracytoplasmic formation are found, it is still not clear what role they play. Are the formation of pathogenic in themselves or are they only a side-product of other mechanisms? The incorporation are present in many areas of the brain. The overall pathology, brain atrophy, particularly in the striatum with all inclusive neuronal loss, is well known.[16]

Pathophysiology :

Due to E.F., Premature death of cells in basal ganglia, Loss of cells in cortex region , Loss of cells in cerebellum, Lack of neurotransmitter like GABA+ Ach, Increase dopamine and abnormal neurotransmission Chorea – Jerky , Involuntary movement, Dementia .HD disease interacts with the two proteins and huntintong's interactor protein (HIP-1) and Huntington's associated protein (HAP-1). These two proteins are present in the brain. The striatum is relaxed of a variety of medium to large neurons that differ in their size and dendritic profile as well as neurochemical content and producing. Medium spiny neurons are inhibitory projection neurons carrying the output of the striatum to the globus pallidus and the substantia nigra and are the major neuronal type, comprising approximately 95% of the neuronal cell in the striatum [17]. The part of the brain most affected by HD is a group of nerve cells at the base of the brain collectively known as the basal ganglia. The basal ganglia organize muscle-driven movements of the body, or ―motor movements‖. The major unit of the basal ganglia are the protease and the put mind (together known as the Striatum) and the globus pallidus (external and internal regions). The clinical symptoms of HD reflect the pattern and the extent of neural loss within different components the basal ganglia-thalamocortical circuit. The neostratum (caudate nucleus and putamen) receives excitatory glutamatergic inputs from the entire neocortex, the first step in the anatomical loop responsible for the initiation and execution of movement.[18].

Neuropathology:

Neuropathological studies come out with atrophy, loss of neurons and gliosis assuredly in the basal ganglia and somewhat less frequently in adjacent structural regions and in the neocortex. Neural degeneration begins are discharge from the striatum, with the original and most severe

ISSN: 0976-7126
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pathology in the mesial region of the tail of the caudate spreading in mesio-lateral and caudo-rostral gradients outward to subregions of the putamen and pallidum with subsequent and more moderate cell loss in the claustrum, subthalamic nuclei and hippocampus (19). Damage outside of the basal ganglia is less consistently observed and the specific relevance of degeneration in other neural networks has thus remained more speculative (20). this caveat in cell loss, mind, however, gliosis and atrophy once a while documented in the spinal cord brainstem, and cerebellum (23) and in neocortical structures, specially the frontal and occipital lobes (21).

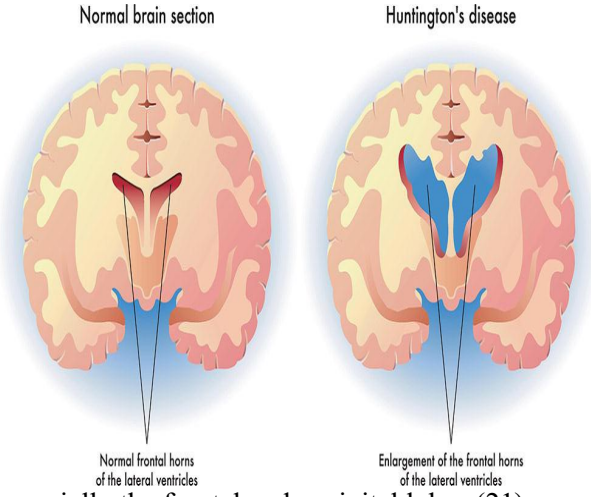

Figure 2: Effect of HD on Brain.

Although a specific link between a particular biochemical abnormality and the pathogenesis of Huntington's disease has yet to be found, neuropathological studies have underscored a role of the small- to medium-sized striatal spiny neurons that contain gammaamino butyric acid (GABA) (36). GABA is a neurotransmitter with a postulated link to the inhibition of spontaneous involuntary movements (22). Also diminished are the concentrations of GABA and its synthesizing enzyme glutamic acid decarboxylase in the striatum, pallidum and substantia nigra and in other basal ganglia and diencephalic structures including the nucleus accumbens, the subthalamic nucleus and the ventrolateral thalamic nucleus (23).

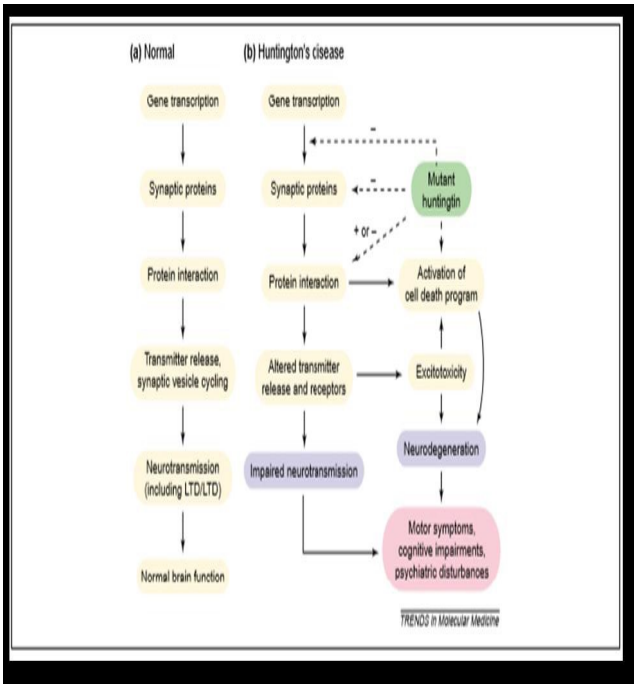

Figure 3: Principal cellular processes involved in the regulation of synaptic transmission. (a) Regulation under normal conditions. (b) Regulation under the pathological influences of mutant huntingtin. The most important take-home message is that not only does mutant huntingtin cause cell death directly, but also it can impair synaptic transmission at several levels, thereby leading to symptoms.

Signs and Symptoms of Huntington's Disease :

The nuclear symptoms and signs of Huntington's disease (HD) consist of motor,behavior and psychiatric disturbances. Other less illustrious, but frequent and generally attenuate features of HD include unexpected weight loss, sleep and day to day rhythm disturbances and autonomic nervous system dysfunction. The mean age at outbreak is between 30 and 50 years, with a range of 2 to 85 years. The mean extent of the disease is 17-20 years. The development of the disease leads to more dependency in daily life and finally death [24].

The motor symptoms and signs

The characteristic motor changes are involuntary, unwanted movements. Initially, the movements generally occur in the distal frontier such as fingers and toes, but also in small facial muscles. For by standers these muscle tremble are generally invisible or can be explained as

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nervousness. In daily life, walking becomes risky and the person can look as if he/she is slightly stoned. moderately the undesirable movements spread to all other muscles from distal to more immediate and essential [25].

No single pattern obtain, but facial chorea tic movements can lead to a continuous movement of facial muscles where for illustrate an eyebrow is lifted, an eye closed, the head is bent or turned while the tongue is beetle with the lips pouting. The most eye catching are the development movements of the long back muscles. Talking and swallowing constantly become more enigmatic leading to choking at any time in some patients. All patients develop akinesia, hypokinesia, and rigidity leading to a slower pace of all activities (bradykinesia: slowness of movement) and a severe hesitation in embarking on a movement (akinesia: difficulty in starting movemevents) [26]. The excess are on the one hand the younger patient with an over overflow rigidity (Westphal variant) and on the other hand the very old patient severely affected in the last stage of the disease with a long duration of bed-bound , illness, with rigidity and flexion counter actives in the adversity. Dystonia can be the first motor sign in Huntington's disease. Dystonia is characterized by sleepy movements with an increased muscle tone leading to abnormal posture, for instance torticollis, but also rotation of the trunk or limbs. Cerebellar signs can appear intermittently, similar to the presence of hypo and hypermetria [27]. Walking is often described as 'drunk' or 'cerebellar ataxia'-like. The extended of motor disturbance on activities of daily life development over time. characteristic between choreatic and ataxic walking is very difficult. Pyramidal signs are present remotely. The presence of hyperkinesias and hypokinesia results in difficulties in walking and standing, and often leads to an ataxic gait and many times falls [28].

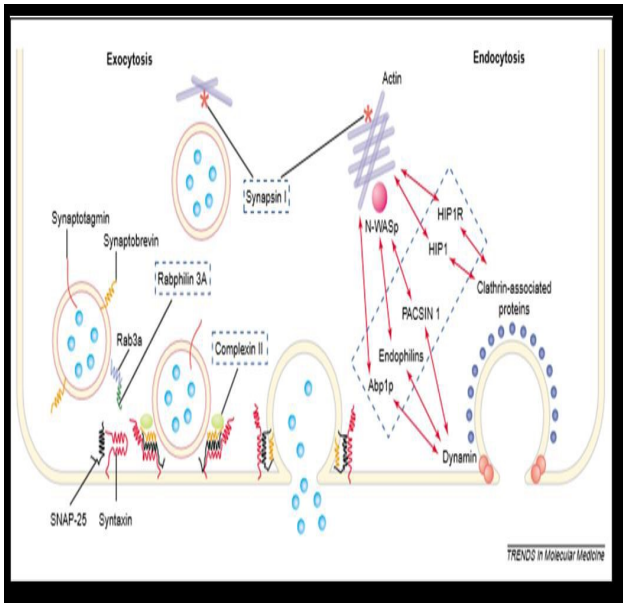

Figure 4: Protein–protein interactions among key factors involved in exocytosis and endocytosis. Red arrows between individual proteins indicate specific binding interactions between those components. Dashed blue boxes indicate protein–protein interactions that potentially could be altered by mutant huntingtin, thereby disturbing endocytosis and exocytosis. Abbreviations: HIP1, Huntingtin-interacting protein 1; HIP1R, HIP1-related protein; N-WASp, neuronal Wiskott–Aldrich syndrome protein; PACSIN 1, protein kinase C and casein kinase in neuron.

Behaviour and psychiatric symptoms and signs

Psychiatric symptoms are very often present in the early stage of the disease, often prior to the access of motor symptoms. The percentage of patients with psychiatric signs varies between 33% and 76% depending on the methodology of the study [29]. these symptoms and signs usually have a highly negative impact on functioning and on the family. The most frequently occurring sign is depression. The diagnosis is difficult because weight loss, lack of interest and inactivity also occur in HD. Around the time of the gene test and the stage when independence decline are the most risky periods for suicide[30]. Usually there is low self- satisfaction, feelings of guilt and anxiety. Insensibility is related to disease stage, whereas anxiety and depression are not. Suicide occurs more often in early symptomatic character and also in premanifest gene carriers. Anxiety also

ISSN: 0976-7126
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occurs often (34-61%), sometimes in relation to unpredictability about the start and or the course of the disease. Phobia and obligation can disturb the patient's life and also lead to irritability and often military [31].

Irritability is often the very first sign, in retrospect, but in fact occurs during all stages of the disease [32]. A loss of activity and increasing passive behaviour are seen as part of the coldness syndrome. Psychoses may appear, mainly in the later stages of the disease. In most cases this goes together with intellectual decline. The complete clinical picture is equivalent to schizophrenia with paranoid and acoustic hallucinations [33].

Dementia :

In normal conditions, cognitive and motor behavior is goal-directed and planned. Normally singleton are able to characterize what is relevant and what can be ignored, but patients with HD lose this capability. Cognitive decline is the main sign of HD and can be present long before the first motor symptoms appear, but can also be very mild in far advanced stages of the disease [34]. The cognitive changes are particularly in relation to ruling functions. Language is relatively spared.

They lose flexibility of mind, and can no longer make mental adjustments. Memory exactly becomes impaired, although the correct memory can be spared to a certain extent. All psychomotor processes become severely retarded [35].

Secondary symptoms and signs :

From previous the unintended weight loss has been reported in all patients. As more attention is now paid to this phenomenon, the loss show to be a little less severe, the cause being diverse. Although it show logical to think that chorea should play the main role in weight loss, it has been shown that there is no relation between weight loss and chorea. A relation with the length of the CAG repeat has been described [36]. Attention has only recently been focused on sleep and circadian rhythm disturbances of patients with HD. More practical issues, such as easy functioning, difficulty handling food and swallowing ,decreased appetite. But hypothalamic neuronal loss is also a causative factor [37].

DIAGNOSIS :

The diagnosis is based on the clinical signs and symptoms in a person with a parent with tested HD. First, it is required to take a microscopic history from the person with symptoms followed by a detailed family history[38]. When all information has been take out the diagnosis is not very serious , although non-specific clinical pictures can be misleading. Also when the parent is not known or has died due to another cause at a young age, the clinical picture can be difficult to remember [39]. It is generally request old information in the form of medical records and autopsy reports. The current gold standard is DNA determination, showing a CAG-repeat of at least 36 on the hunting tin gene on chromosome 4 [40].

Before 1993, a family history with clinical and morphological verification in at least one of the parents or grandparents was required. The clinical criteria currently necessary are still motor changes with or without psychiatric or cognitive changes. However, in most cases a combination of the three main signs is present. The combination with the family history is sufficient for diagnosis. No imaging, general blood tests or other diagnostic tools are helpful.

Extensive studies are underway to detect biomarkers (clinical, blood, MRI) and hence the transition determining parameters [41].

Differential Diagnosis :

When chorea is the presenting and most prominent signand symptoms, taking a history is the first and very useful step. The frequently occurring differential diagnoses for motor sign chorea. In many cases the underlying cause is another general internal disorder. Only very few genetically determined disorders are responsible for chorea tic syndromes. [42]

Table 1 Differential Diagnosis for chorea [43]

Hereditary - Huntington's disease
- Benign hereditary chorea
- Neuroacanthocytosis
- DentatoRubroPallidoLuysianAtrophy (DRPLA)
- Wilson disease

Rheumatic disorders - Sydenham chorea
- Chorea gravidarum

Drug-induced - Neuroleptic drugs
- Oral anticonceptive drugs
- Phenytoine
- Levo-dopa
- Cocaine

Systemic disorders - Systemic Lupus Erythematodes (SLE)

- Thyrotoxicosis
- Polycythemia vera
- Hyperglycemia
- AIDS
- Paraneoplastic

Genetic Counselling :

When the gene was localized on chromosome 4 in 1983, premanifest diagnosis became available for the first time using linkage analysis. Linkage analysis provided the applicant with results, initially with a certainty of 93% and later with a certainty of about 98%. [44].

standard procedure was the following: step 1, consultation with a clinical geneticist and preferably in combination with a psychologist and a neurologist. After 4-6 weeks a second consultation (step 2) takes place including blood sampling. After a period of 6- 8 weeks a consultation (step 3) with disclosure is planned. Exclusion criteria for the procedure are: age below 18 years, severe psychiatric illness, and external pressure for the applicant. [45].

Table 2: Differential Diagnosis for chorea. [46]

Hereditary	**-Huntington's disease**
-Benign hereditary chorea	
- Neuroacanthocytosis	
-DentatoRubroPallidoLuysianAtrophy (DRPLA)	
- Wilson disease	
Rheumatic disorders	- Sydenham chorea
- Chorea gravidarum	
Drug-induced	- Neuroleptic drugs
- Oral anticonceptive drugs	
- Phenytoine	
- Levo-dopa	
- Cocaine	
Systemic disorders	- Systemic Lupus Erythematodes (SLE
- Thyrotoxicosis	
- Polycythemia vera	
- Hyperglycemia	
- Paraneoplastic	

Prenatal diagnosis :

the test can be performed on any cell with a nucleus containing DNA, antenatal diagnosis is also possible. Between the 10th and 12th weeks of pregnancy, chorionic house sampling and between the 15th and 17th weeks amniocentesis can be performed and DNA-testing carried out[47]. The procedure is only start if the parents already know their own genetic status to prevent unwanted informing for two individuals at the same time. The procedure is get on with the intention of ending the pregnancy if the HD gene is found in the embryo [48]. The mother cannot be forced to agree with this conclusion. If the parents have not yet been genotyped, one can opt for an situation test by comparing the genetic status of the embryo with that of the grandparents. In this situation the result is either 0% risk for the foetus, and so the parent keeps his or her 50% status, or 50% risk for the foetus. The foetus has received a chromosome from the affected grandparent, but it is not known to which chromosome the HD gen is coupled. In this case the foetus has a 50% risk, comparable to the parent, and the parents can decide to abort a 50% at risk baby. During the last decade, preimplantation diagnostics has also been offered in many countries. The procedure starts with in vitro fertilization[49].

Symptomatic Treatment of Huntington's disease

Although many signs and symptoms can be treated, it is not always necessary to do so. The patient's limitations in daily life determine whether or not drugs are required. Very little evidence is available about the drug or the dosage to prescribe for any signs and symptoms[50]. Drug treatment is, therefore, individualized and based on expert opinion and daily practice. Treatment consists of drug prescription and non-medication advice. Surgical treatment does not play an important role in HD [51].

Rehabilitation:

Psychotherapy- A Psychotherapist can provide talk therepy to help a person manage behavioral problems, developing coping strategies.

Speech therapy- A speech therapist can help improve ability to speak clearly or teach to use communication devices- such as board covered with pics of everyday items.

Physical therapy- A Physical therapist can teach appropriate and safe exercises balance and co-ordination.

Occupational therapy- An Occupational therapist helps patient in use of assistive devices that improve functional abilities [52].

Conclusion

Since the first clinical stage of Huntington's disease, both the clinical and neuropathological parameters have become increasingly defined and the responsible gene itself has been isolated. the etiology of the disease and its pathogenesis continue to be poorly understood and current treatment approaches have remained relatively primitive.The energy metabolism model, particularly when combined with excitotoxicity hypotheses, may provide a mechanism for the age-related expression of selective cell death occurring in this disease. Although clinical trials have yet to support a safe and effective therapeutic agent, an increased understanding of the pathophysiology and molecular biology of the disorder may well offer new treatment avenues. The current use of positron emission tomography and the future applications of functional magnetic resonance imaging will, without doubt, provide critical insights into the nature and expression of the degenerative process. This may well further clarify brain-behavior relations when considered within models of basal ganglia circuitry and combined with improvements in the description of the course and manifestation of the clinical pathology.

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Cite this article as:
Gupta D., Shrivastava S.K., and Malviya R.K (2021). Huntington’s disease: Pathophysiology, Diagnosis, Treatment and Rehabilitation. *Int. J. of Pharm. & Life Sci.,* 12(11):17-26.

Source of Support: Nil
Conflict of Interest: Not declared
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