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A Short Review on Rare Neurodegenerative Disorder: Huntington's Disease

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Abstract
In recent years we are getting aware of many rare incurable diseases which lead to the sudden changes in our body that promotes to death. Huntington's disease is one of the rare inherited, progressive neurodegenerative diseases consisting of different symptoms like chorea, dystonia, ataxia, mania and psychosis. It was the first trinucleotide disease to be described. In this review we provide the information about the disease and the research activities done which will help to identify the major findings in pathological, diagnostic and treatment ability of Huntington's disease using different methods.

Keywords
Chorea, neuronal loss, trinucleotide, Huntington's, Mania.

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INTRODUCTION
Huntington's disease (HD) is a progressive neurodegenerative disorder exhibiting typical cognitive, motor and maniac symptoms [1]. It is caused by an expanded unstable CAG trinucleotide repeat within the coding region of the *HD* gene [2]. Movement disorders are predominant in early middle life due to neuronal loss, that undergo chorea and dystonia inevitably leading to death within 15 to 20 years, in rare cases it may be seen in juveniles [3,4]. Striatal region and a basal ganglia part are the main neuronal loss areas in according to the HD that shows lack of coordination in voluntary and involuntary movements [5]. The CAG repeat in HD gene contains an abnormal long polyglutamine (polyQ) which is referred as mutant Huntington. Mutant having toxic properties causing death of neurons. Expansion of polyQ HTT responsible for cytotoxic and biological dysfunctions observed in HD models [6, 8]. Awareness among the people about this disease has increased as the disease of the whole brain and body. Neurodegeneration due to this condition has no therapies still now to minimize the loss of lives.

Historical Approaches:
In 1872 George Huntington a physician was first to identify this disease as movement disorder by delivering a paper named 'On Chorea'. In this he explained all the clinical features like choreiform movements, cognitive impairments and behavioral changes which occur in the diseased person. Later that J. Hoffman identified the clinical features described by the G.Huntington is similar in adolescents by observing the data of three generations of a family. He also explained that the symptoms seen in adults are different from

adolescents and termed as 'Juvenile Huntington disease' [9]. From here several findings were made to identify the molecular pathogenesis of the disease later on 1980's mapping of HD gene was carried out. In early days researchers tried to analysis the causative of HD by some methods like neurotoxin mediated striatal lesionong to identify the damaged area of brain. For this they have introduced some of the neurotoxins like ibotenic acid and kainic acid which damage the nerve cells in striatum. Later administration of mitochondrial toxins such as malonate and 3-nitropropionic acid (3-NPA) were used to generate lesion models causing straital damage in brain. Mitochondrial toxin-induced striatal lesions were also used as acute models of HD in rodents and non-human primates. Progressive, age-dependent pathogenic events cannot be represented in the acute lesion models. Finally, the restricted pathology caused by striatal lesions, many of the neurological manifestations of HD that are caused by pathology in other parts of the brain are not reproduced in the lesion models [10, 11]. Till 1991 reason for the CAG repeats were unknown, different trails were made to explain the CAG repetitions in HD. In between the findings of HD mutation different genes were known which cause CCG expansion of FRAGILE X SYNDROME [12] CAG expansion of Spinal and Bulbar Muscular Atrophy [13] and CTG expansion of Myotonic Dystrophy [14]. After these findings Huntington disease-associated alleles and unaffected CAG-repeat distributions were defined. The unaffected range is (CAG) 6–35 repeats, alleles of (CAG) 40 and above are fully penetrate and cause Huntington. There is an inverse relationship between the age of onset of Huntington disease and the CAG repeat size, with alleles of (CAG) 70 repeats and above invariably causing a juvenile onset [15, 16]. Few years later polyglutamine containing repeats in the pathogenic range, could spontaneously aggregate into amyloid fibrils *in vitro* has shown in protein encoded by exon 1 of the HD gene [17, 18]. Then many doubts raised based on the stages of misfoldings and aggregation pathways. In 1996 the first mouse model of Huntington disease was generated which the neuropathological observations have done by isolating the mouse brains and it revealed the ubiquitylated protein information about the pathogenesis of HD indicating the transcriptional dysregulation as early sign of this disease [19]. Since then different types of" Knock-in" and mouse models have been generated to overcome the mechanism of Huntington's disease. An inducible mouse model created by Ai Yamamoto in 2000 which exon 1 of the *HD* gene with (CAG) 94 repeats could be switched off after adding doxycycline to the drinking water [20]. His study brought a remarkable change in the findings of pathogenesis that symptoms of Huntington aggregates were cleared from mouse brains and motor coordination were reversed indicating that early stages of Huntington's disease can be treated. A number of genetic approaches have been used to generate animal models of HD. use of full-length or only a fragment of mutated gene. *C. elegans models* showed age-dependent mechanosensory defects, dysfunction of neurons and neurodegeneration. *D. melanogaster models* the HD fly models exhibit a progressive degenerative phenotype as well as motor abnormalities and reduced survival. *Rodent models.* All of the truncated N-terminal fragment models typically exhibit a rapid onset of symptoms, including motor, cognitive and behavioural abnormalities, weight loss and a reduction in lifespan. These symptoms are accompanied by a widespread and generalized degenerative phenotype [21].

Pathological Findings:

According to the Neuropathological studies Huntington's disease have notable cell loss and atrophy in regions of caudate and putamen of basal ganlia [22–23]. Medium spiny neurons present in the srtaiatal regions are more susceptible containing encephalin and substance P on external and internal globus pallidum [22]. Cells present in the cortex layers 3,5,6 and the hippocampal CA 1, substantia nigra which is part of a mid-brain and the angular gyrus [25,26] in parietal lobe and the purkinje cells [27] regions of hypothalamus [28] will get damaged. Cortical neurons present in the layers of cortex shows less number of cells which disintegrate nerve fibers, neurofilaments, tubilin and associated protein [29,30]. Synptic function, cytoskeletal integrity and axonal transport is based on these neuronal concentrations of cortical dysfunction. Presence of nuclear, mHtt and polyQ in cytoplasm are one of the cause for huntingtons disease [31]. PolyQ indicates selective neuronal dysfunction and seems to involve proteolysis and aggregation in the Huntington [32]. Replacement of proteins facilitate aggregation in mutant Huntington which reduces stertic interface and those are toxic, which have to translocate the nucleus [33,35]. According to other mechanisms mHtt affects nucler and cytoplasmic proteins which regulate apoptosis [36], mitochondrial function, tumour suppression, vesicular and neurotransmitter release by this mHtt exerting dominant negative effect with toxic function [36,38]. Another step in the pathogenesis of Huntington's disease might entail

cell-cell interactions. Mutant huntingtin might cause harm to a neuron, by disrupting the function of nearby neurons or glia that provide important support to that neuron [39]. Oxidative stress also plays a major role in neurodegeneration in HD by forming intercellular cascades that leads to lipid peroxidation (LPO) in cellular membranes by oxidizing proteins and DNA. The levels of LPO has been recently found in transgenic and knock-in mouse models of HD, the specific antioxidant proteins change the toxicity of mHtt in cultured neurons [40,41]. Recent studies have shown a significant increase in the oxidative damage in HD brain. Mitochondrial dysfunction is primarily related with the oxidative stress in which the activities of mitochondrial complexes ii/iii and iv frequently reported in caudate and putamen of HD patients [42,44]. Both the mitochondrial dysfunction and oxidative damage can be produced by administering mitochondrial toxins 3-Nitropropionic acid or malonate which causes straital damage in brain closely similar for observation [45]. However, the mechanism of the pathologic process is going on to observe the mitochondrial and oxidative damage in HD.

Symptoms

Different types of symptoms are seen in the Huntington's disease which effect the daily activities of life they are

a. Motor Symptoms

Generally motor dysfunction is widely seen in individuals of HD as they are involuntary movements which looks like dancing often called as chorea. 90% of the patients are seen with the choreatic symptoms [46] looks like slightly drunk, firstly these movements occur at fingers and toes later extend to the facial muscles similar to paralysis. A slower movements of voluntary muscles, becomes more rigid in later stages resembling bradykinesia [47]. Other signs of motor deficits like Dystonia, an involuntary muscle contractions causing twists and abnormal postures. Dysarthria, is one of the early symptom of speech abnormality and also difficulties in walking and standing which refers to cerebral ataxia [48]. Dysphagia, is also a symptom having difficult in swallowing will develop in advanced stages [49].

b. Cognitive Symptoms

In HD gene cognitive functions can be detected mainly that exhibit impairments in execution of function, lack of attention, concentration and memory loss [50]. It also includes language related problem showing the sign of disturbance in the ability of thinking and unable to remember the things happened before. Storage of memory will be decline, lowering thoughts, even unable to retrieve information regarding past event. It is the sign of the HD which diminish the individual in every aspect of cognitive features; they will lose all information regarding vital functions in our daily life. They are unable to think, organize and planning of any other actions. Detailed neuropsychological tests reveal that patients with HD exhibit impaired visuospatial abilities [51].

c. Behavioral and Psychiatric Symptoms

Continuations to motor disturbances psychiatric symptoms are very frequently present in the early stage of the disease. These are clinically diagnosed based on the psychiatric movements like anxiety, impulsivity, aggression, irritability and depression [52]. Patients with HD regularly effect with depression moreover, hallucinations and psychosis occur in patients of advanced stages. Finally, suicide is more common in patients with HD than in the general population [53]. A loss of interest and increasing passive behavior are seen as part of the apathy syndrome. Usually there is low self-confidence, feelings of guilt and anxiety. The complete clinical picture is comparable to schizophrenia with paranoid and acoustic hallucinations.

Treatment:

Different drugs are used to treat the symptoms of Huntington's. Tetrabenazine is the drug used for the treatment of chorea which is approved by the USFDA recently but it exhibits the adverse effects like depression and sedation. For the treatment of symptoms like rigidity, dystonia and spasticity drugs like clonazepam, levodopa and tinzanidine are using but they are having some disturbances on the other area of body. And the remaining symptoms like Depression, anxiety, psychosis, irritability, altered sleep and Mania, are also treated with different drugs such as citalopram, fluoxetine, zolpidem sodium valproate, carbamazepine which are having the side effects like GI disturbances, hypersensitivity reactions, drowsiness, confusion, memory disturbance and postural hypotension. Hence every drug having a chance to treat only a particular symptom in HD.

Future Perspectives

Over the past decades, awareness about the rare incurable diseases was increased due to the continuous efforts of the researchers all over the world. Different trails were done on the Huntington's disease, a rare progressive neurodegenerative disorder causing polyglutamine expansions where the treatment is limited to identifying and controlling some of the symptoms. HD gene models and the

inducible mouse model provide the chance of lowering the symptoms by using some of the drugs which can treat progressive situations. HD is a lifelong disease for both the individual and the generations of family. Focus on the pathophysiology of the disease was started in 1983 when the gene was localized, particularly in 1993 for giving a way to find the first autosomal dominant disease where premanifest diagnosis became possible. Some of the transgenic models tried to analysize the causative of HD. However, the findings of the research provide the information about the symptoms of the Huntington. A better understanding of the Pathophysiology will surely lead to drug development to interfere in the pathological process. As per available literature a few symptoms like chorea, psychosis, dystonia can be treated alone in HD but they are unable to treat the whole disease. The developments are promising to find out the drugs from natural sources, marine sources.

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