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HUNTINGTON'S DISEASE: UNDERSTANDING THE PATHOPHYSIOLOGY THROUGH THE HUNTINGTIN GENE

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Abstract:

Huntington's Disease (HD) is a progressive neurodegenerative disorder. It is an autosomal dominant disorder that is categorized by motor dysfunctions, behavioral and cognitive deficits. Reason for this disease is expansion of the polyglutamine (due to the more CAG repeat) in the amino-terminal region of the exon 1 of the Huntingtin gene (HTT). Furthermore, the mutant HTT gene is occupied in the HD associated changes of neurotransmission for enabling the neurodegeneration. Even though the the important pathophysiology of the HD happens in the caudate and putamen, rest regions of the brain are similarly influenced and also show a significant characteristic in the HD pathophysiology. Until now actual remedy for the HD is not available. As a result, current approaches are directing to the HTT gene expression silencing. It is now taken as the probable way of the management of HD. But the most important thing is, core functions of the HTT gene in the brain of adult subject are presently not clear at all and henceforward the outcome of the continued HTT gene expression suppression of is unpredictable. It could be possibly being tough. This review is based on the pathophysiology of HTT on HD.

Keywords: *huntington's disease; Neurodegenerative Disorders; Pathophysiology; Huntingtin gene*

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INTRODUCTION:

As a gift of astute devotion by an American physician George Huntington, the Huntington's Disease (HD) was first revealed in 1872. It is also known as Huntington's chorea [1]. HD is an autosomal dominant, fatal, progressive neurodegenerative disease due to codon CAG expansion in respective gene [2]. This disease is monogenetic in nature [3]. From environment, genetic and pathogenic factors, this disease causes a complex nature [4]. To find out the pathophysiology and management of this disease, the scientific community is facing various challenges [5,6]. By doing research on this, Eric Betzig, Stefan W. Hell and William E. Moerner had been awarded the Nobel Prize in Chemistry for 2014. They made microscopic method for tracking proteins involved in HD [7]. Patients having HD show different behavioral changes at the time of disease progression. Severe psychosis, subtle anxiety and suicide attempts are among them [8]. But the vital fact is the decline in cognitive function. This decline usually begins at the early in the development of this disease and progress over time. Yet the actual progressive profile of cognitive decline over time is unidentified and a huge measures have been conducted to recognize the pathophysiological mechanisms [9,10]. At middle age, symptoms of HD usually seem. Yet, HD can start earlier, and about 6% grow at juvenile conditions. The immense damage of neurons in striatum region is accountable for facilitation of movement, is supposed to proceed to the characteristic motor dysfunctions of HD. The preliminary signs differ in individual but the primary stage of the disease is generally noticeable by thorax associated with progressive emotional, involuntary movements of the face, fingers, feet or psychiatric, and cognitive disturbances. Psychiatric symptoms include depression, anxiety, apathy and irritability. Furtherly, HD is categorized by motor signs (rigidity and akinesia), liberal dementia, or continual weakening of the mental procedures associated in comprehension, intellectual, decision making, and reminiscence [11]. Weight loss, changes in sensual behavior, and troubles in the sleep cycle are other features of this disease. It can be elucidated by hypothalamic dysfunction. Patients with HD typically dies in 15 to 25 years later the initial symptoms seem, as there is presently not any exact treatment to withdraw or delaying disease development [12]. Here in neostriatum, the gross atrophy of the caudate nucleus and putamen is convoyed by specific neuronal loss and astrogliosis. Moreover, a good neuronal damage also is seen in the deep layers of the cerebral cortex. On another region, including the thalamus, globus subthalamic nucleus, pallidus, substantia nigra, and cerebellum, show changeable grades of atrophy depending on the pathologic condition [13,14]. The degree of total neuronal loss, striatal pathology, and gliosis delivers a basis for grading the severity of HD pathology. As genetic basis of HD is the enlargement of a cysteine-adenosine-guanine (CAG) repeat encoding a polyglutamine tract in the N-terminus of the protein product called huntingtin (HTT) [15].

SYMPTOMS IN THE MOTOR:

In the severe locomotor problem with hyperkinesia symbolizes the HD. These automatic movements have been got first in the fingers and toes, then in the trunk. Around 10% of wholly patients having HD may, nevertheless remain the juvenile onset or Westphal abnormal of HD with indications of hypokinesia and also rigidity similar to the Parkinson's disease. Complications with the steadiness done, with exaggerated fiddling motor action and a chance to violent automatic activities. HD patients frequently walk through a dance-like step with legs broadly separated to recompense for the deficiency of balance and regulator. The indications may originate the patient to seem to be befuddled by alcohol. Nearly entirely patients apparent irregularly timed, casually distributed and unexpected choreatic activities [16]. They also may have their hands in the pockets for limiting irrepressible arm movements. With distinctive chorea of the face, facial musculature is attacked and show in the form of elating of the eyebrows, puckering of the lips, glowering and sleepy head movements. Eye actions have become troubled at initial period along with spasmodic action. The patients have trouble in focusing the eyes on rotating matters. Fine motor skills weakening, categorized by gaucherie and complications with acquisitive and holding substances [17]. Cognition in Huntington's disease patient may be diagnosed when subtle neurologic symptoms are identifiable as disturbed tongue and eye movements.

VARIATIONS IN THE PATHOPHYSIOLOGY:

An extensive discerning neuropathology is found in HD through cell loss and atrophy. The variations are amazingly specific in their effect on exact brain cell categories and specific brain assemblies. Average gamma-aminobutyric acid (GABA) spiny neurons are the neuronal cells mostly exaggerated, largely in the caudate nucleus and putamen. The cortex is less affected and the cerebellum is relatively spared. The HD gene product, a very large 350 kDa protein known as huntingtin. It is supposed to have a poisonous effect which leads to cellular dysfunction and eventual death of neurons [18]. The exact mechanism of the toxic effect is still poorly

understood. Early neuropathological changes are seen selectively in the striatum, where 90% of neuronal cells are medium spiny projection neurons also known as MSP neurons. Loss of projection neurons in the caudate nucleus is the dominant neuropathological change. Death of neuronal cells continues gradually in layers 3, 5 and 6 of the cortex, the substantia nigra and the CA1 region of the hippocampus. Loss of enkephalin-withholding MSP neurons in the striatum, which indirectly controls voluntary and related movements, constitutes the neurobiological basis for HD chorea. The preferential involvement of the indirect pathway of basal ganglia-thalamocortical circuitry is believed to be the cause of chorea. Fronto-striatal circuitry linking the striatum with frontal lobes is also affected [19]. In addition, changes in the substantia nigra, hippocampus, hypothalamus and selectively in the cortex and white matter are found [20].

VARIATIONS IN THE CHEMICALS:

Large atrophy in the vast parts of the brain has been seen in the final period of HD. Neuronal damage leads to decrease of neurotransmitters like - gamma aminobutyric acid (GABA), peptides (e.g. enkephalin), glutamic acid decarboxylase (GAD), (ChAT) in the striatum [21]. Moreover, glutamate and choline acetyltransferase and there is an increase in the level of serotonin. However, density of the serotonin receptor decays. A decrease in postsynaptic dopamine receptors D1, D2 and in the dopamine transporter DAT in the striatum similarly takes the latent to elucidate the cognitive deficiencies of patients with HD [22]. The complex and multifarious symptoms of HD have been attributed to these neuropathological and neurochemical changes.

SIGNIFICANCES OF THE POLYGLUTAMINE EXPANSION FROM THE MUTANT HUNTINGTIN GENE

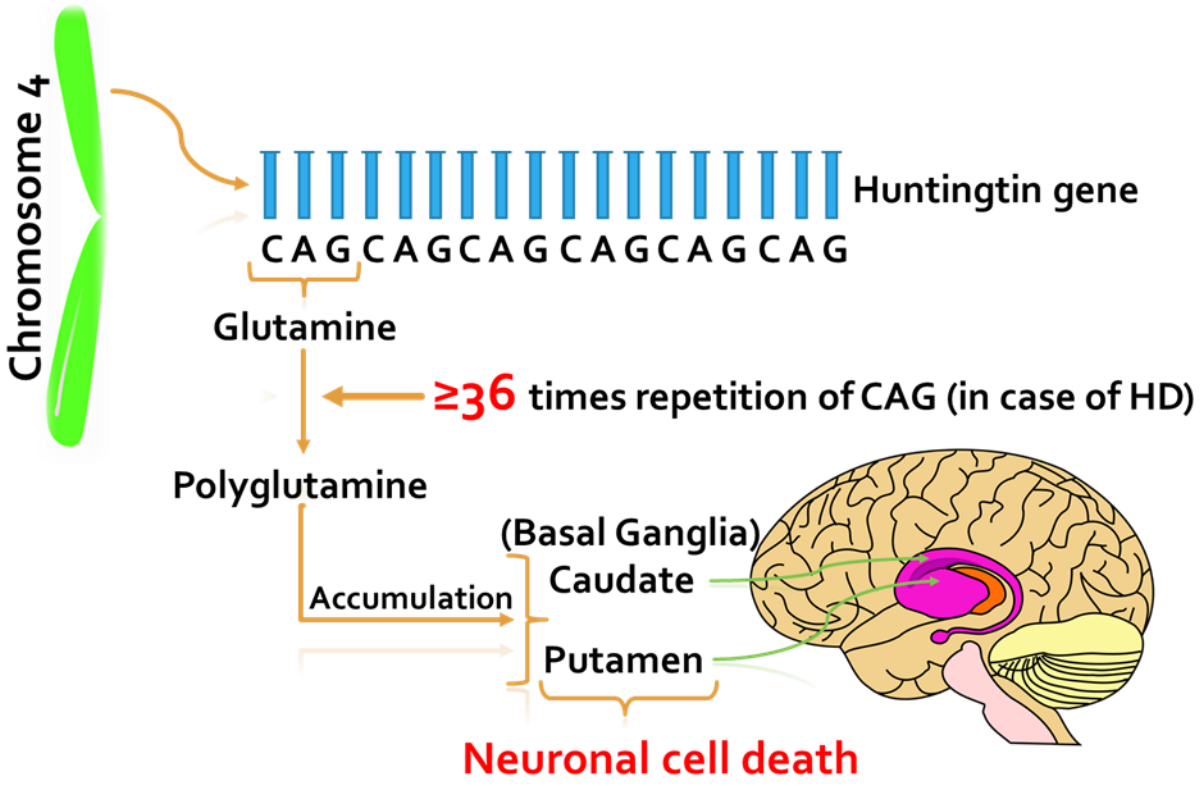

Fig.1: Ways of polyglutamine accumulation in the basal ganglia (specially in caudate and putamen) which further leads to neuronal cell death.

HUNTINGTIN WITH THE AFOREMENTIONED ROLE:

Though the huntingtin gene was exposed many years ago but the physiological character of the protein only has just started to be clear now [23]. Huntingtin is far and widely expressed. Inside the neurons, huntingtin is situated in the cytoplasm and inside the neurites and also at synapses. It links through numerous organelles and structures as like endosomal and endoplasmic compartment, clathrin-coated vesicles, microtubules, mitochondria and plasma membrane [24]. Though largely spread in the cytoplasm, huntingtin is noticed in the nucleus also. Assumed its subcellular localization, huntingtin seems to pay to several cellular activities in both cytoplasm and nucleus. Besides, huntingtin relates with many proteins associated in the gene expression, intracellular signaling, intracellular transport and metabolism. A clear feature of the HTT protein is the polyQ stretch at its NH2 terminus [25].

HUNTINGTIN FUNCTION AT THE DEVELOPMENT AND NEUROGENESIS:

At the primary developing embryo, HTT is extensively regulated wherever this function in some methods as well as cell neuronal survival and differentiation [26]. In the subject gene, inactivation consequences in developing delay in addition embryonic lethality. Due to early patterning of the embryo, HTT is important throughout the construction of anterior area of the primitive streak. By means of the advance of embryonic growth, investigational decreases of HTT levels under 50 percent originate problems in the epiblast creation and the shape which would provide upsurge to the neural tube. Other defects also seen like deep striatal and cortical architectural disturbances.

HTT is associated in the neurogenesis is revealed specifically in recent studies [27]. Cancelations of HTT in the murine cortical progenitors alter characteristics of the cleavage division. It decreases the pools of basal and apical progenitors simultaneously as well as rises daughter cell's neuronal differentiation [28]. For this, the decreased level of HTT in the mouse, severe anatomical brain abnormalities had been seen. At the mitosis stage, HTT places exactly at spindle poles also links through some component of the mitotic spindle. If HTT silenced then it altered the orientation in the spindle by modifying its strength. Moreover, it disrupts the correct placement of various important components.

ANTI-APOPTOTIC CHARACTERISTICS OF HUNTINGTIN:

It is thought that HTT has a pro-survival character. By the knock-out mouse models, it had been shown that primarily the high level of apoptosis which is an anti-apoptotic feature of HTT. Regulation of the total protein is secured from different type of apoptotic stimuli and this is validated from numerous in vivo and in vitro investigations. By the continual rise in the level of HTT, an improved neuroprotection had been seen. This shows the consequence of gene-dosage. Numerous molecular mechanisms based on the pro-survival actions of HTT had been explained. HTT seemed to function downregulation of mitochondrial cytochrome c release, preventing the activation of caspase-9 and caspase-3 [29]. HTT actually interrelates with energetic caspase-3 and hinders the activity. HTT may also avoid the creation of the complex HIP1-HIPP then the consequent initiation of caspase-8 by impounding HIP1. To the end, HTT shows antiapoptotic activity by adding to Pak2 (p21-activated kinase 2) [30]. It decreases the aptitudes of the caspase-8 and caspase-3 for cleaving Pak2 and change this into a medium of the death of cell [31].

TRANSCRIPTION OF HUNTINGTIN:

Roles of HTT in transcription are sound recognized. HTT had been revealed to relate with good quantity of transcription factors like the co-activator CA150, p53 and also transcriptional co-repressor C-terminal binding protein (CtBP). HTT triggers transcription through possession of REST inside the cytoplasm, far from the nuclear target. The neuron preventive lowering element, a consent order had been observed in numerous genes. Steadily, more expression of HTT tends to a rise in the mRNAs whose are transcribed from several neurons preventive lowering element. HTT has not been seemed to relate with REST independently, but then goes to a compound that is having dynactin p150 Glued and RILP (REST-interacting LIM domain protein), HAP1 (HTT associated protein 1), a protein that straight fixes REST and encourages the nuclear translocation. HTT also consequently performed in the body nervous system like a common organizer of different transcription of neuronal gene for a genes subclass. specifically, HTT controls the construction of BDNF, also a neurotrophin vital for the existence of striatal neurons. For this reason, this is important. It is revealed by different investigations in the zebrafish displaying that damage of BDNF recaps maximum

developing problems realized with the knockdown of HTT. It is also seen that the contact of HTT through both HAP1 and MLK2 helps in the NeuroD expression. HTT helps domination of the transcription of gene by interacting to repressor compound having Sin3A and N-CoR.

INTRACELLULAR TRANSPORT OF HUNTINGTIN:

HTT is mostly available among the cytoplasm where this contacts through vesicular shapes, microtubules. HTT contacts through numerous proteins which play function in the intracellular trafficking. HTT relates through dynein and also the HAP1 (HTT-associated protein-1). It is a protein which connects with the subunit p150 Glued dynactin, a vital constituent of dynactin microtubule-based motor complex. primary record of the activity of HTT in the intracellular transport derived after the investigation in Drosophila which showed that the decrease in HTT gene expression caused in the axonal transport faults in their larval nerves. It also showed neurodegeneration in the eyes (adult). it has been established by the additional investigations in the mammals. First it has been shown that wild-type HTT stimulates transport by binding with HAP1 and subsequently interacting with the molecular motors dynein/dynactin and kinesin. HTT directly promotes the microtubule-based transport of BDNF and Ti-VAMP (tetanus neurotoxin-insensitive vesicle-associated membrane protein) vesicles in neurons through this interaction. Second, it has been shown that fast axonal trafficking of mitochondria was altered in mammalian neurons expressing less than 50% of wild-type HTT. Accumulating or decreasing HTT in cells increases or reduces the speed of intracellular transport, respectively. Thus, this suggests that HTT is a processive factor for the microtubule dependent transport of vesicles. In particular, decreasing HTT levels in cells alters the interaction of the anterograde molecular motor kinesin with vesicles, whereas the direct interaction of HTT with dynein facilitates dynein-mediated vesicle motility. Finally, phosphorylation of wild-type HTT at S421 is crucial to control the direction of vesicles in neurons. When phosphorylated, HTT recruit's kinesin to the dynactin complex on vesicles and microtubules and therefore promotes anterograde transport. Conversely, when HTT is not phosphorylated, kinesin detaches and vesicles are more likely to undergo retrograde transport.

SYNAPSES AND ENDOCYTOSIS:

HTT acts through several proteins which regulates both endocytosis and exocytosis like HIP1 and HIP14, HIP1R, protein kinase C, and PACSIN1 [32]. From the Golgi region, HTT is altered with the HIP14 protein; a palmitoyl-transferase associated with containing of numerous proteins. HTT is significant for the function of Rab11, a critical GTPase in regulating membrane traffic from recycling endosomes to the plasma membrane [33]. The Rab11 nucleotide exchange activity is altered in cells depleted for HTT suggesting a role for HTT in Rab11 activation. HTT may also take part to the presynaptic complex through its interaction with HIP1, which has been associated with the presynaptic terminal. Furthermore, HTT can bind to PACSIN1/syndapin, syntaxin, and endophilin A, which collectively play a key role in synaptic transmission, as well as in synaptic vesicles and receptor recycling. Finally, wildtype HTT interacts with postsynaptic density 95 (PSD95); a protein located in the postsynaptic membrane) through its Src homology-3 (SH3) sequence, regulating the anchoring of NMDA and KA receptors to the postsynaptic membrane [34–37]. At the postsynaptic membrane, HAP1 binds Duo (the human orthologue of Kalirin) that is known to activate Rac1 signalling that plays an important role in the remodelling of the actin cytoskeleton. Thus, HTT might modulate Rac1 signalling and actin dynamics in dendrites via its interactions with HAP1 and PSD-95. This is further supported by the reported interaction of HTT with Cdc42-interacting protein 4 (CIP4) and FIP-2, two proteins involved in actin dynamics and dendritic morphogenesis in the postsynaptic density [38,39].

SOLUTIONS AND RECOMMENDATIONS:

Some clinicians use different FDA approved drugs including deutetrabenazine or tetrabenazine [40]. They are from the vesicular monoamine transporter 2 (VMAT2) inhibitor group [41]. Moreover, stabilizers of dopamine like pridopidine in addition other drugs under experimentation are also at present being studied for the management of HD.

FUTURE RESEARCH DIRECTIONS:

There are lots of opportunities to work to find the specific pathophysiology due to the lack of sufficient data regarding this and determine the exact mechanism of HD [42,43]. Like how gene of HD expansion carriers related with the CAG length through their cognitive profile and more [44].

CONCLUSION:

If it is being possible to find the accurate scenario behind pathophysiology of HD, then choosing medicaments of HD will be a matter of time. More concentration should be paid for revealing the pathophysiology. Then treating most important

deficit oriented with HD, cognitive impairment can be easier than ever before.

ABBREVIATIONS

HD: Huntington's Disease; HTT: Huntingtin; NDs: Neurodegenerative Disorders; CAG: Cysteine-Adenosine-Guanine; HIP: HTT-Interacting Protein; BDNF: Brain-Derived Neurotrophic Factor Protein; HAP: HTT-Associated Protein; HIPPI: HIP1 Protein Interactor; GABA: Gamma Aminobutyric Acid; GAD: Glutamic Acid Decarboxylase; HIP1R: HIP1-related protein; PACSIN1: Protein Activation casein kinase Substrate in Neurons-1; KA: kainite; PSD95: Postsynaptic Density 95; SH3: Src homology-3; CIP: Cdc42-Interacting Protein; NMDA: N-methyl-d-aspartate; VMAT2: Vesicular Monoamine Transporter 2.

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