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Homocysteine Induced Neurological Dysfunctions: A Link to Neurodegenerative Disorders

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ABSTRACT

Excessive level of Homocysteine (Hcy) is considered a neurotoxin since it has a very deleterious effect on the nervous system. It is a sulfur-containing amino acid that is reversibly formed and secreted during metabolism. Pre-clinically and clinically, Hcy exhibits several neurological mechanisms that have been reported in the pathogenesis of Alzheimer's disease, stroke, Parkinson's disease, multiple sclerosis, epilepsy, neuronal cell death, and amyotrophic lateral sclerosis. Homocysteine may promote Alzheimer's disease by more than one mechanism, including oxidative stress, neuronal cell damage, tau phosphorylation, enhancement of beta-amyloid aggregation, and hyperactivation of NMDA receptor. Moreover, it increases the production of chemokines by stimulation of nuclear factor-kappa B. It is well known that the use of levodopa diminishes the symptoms of Parkinson's disease but also lead to an elevation in the level of homocysteine. In this review, we highlight the associate relationship between hyperhomocysteinemia and neurological disorders by discussing its neurodegenerative effects.

Keywords: Homocysteine, Neurodegenerative disorder, Alzheimer's disease, Stroke, Parkinson's disease, Multiple sclerosis

INTRODUCTION

Homocysteine is a sulfur-containing amino acid derived from methionine, and its plasma concentration is regulated by either remethylation or transsulfuration pathways. Homocysteine is converted back into methionine with the help of betaine-homocysteine methyltransferase or methionine synthase and cobalamin (remethylation pathway). Homocysteine is converted to cystathionine by the action of cystathionine beta-synthase (CBS) with pyridoxine acting as co-factor (Figure 1). Homocysteine acts as a precursor and metabolite to S-adenosyl methionine (AdoMet) and S-adenosyl homocysteine (AdoHcy) respectively [1]. The ratio of these 2 is referred to as methylation potential (MP) [2].

As stated earlier, AdoHcy when in high concentrations competes with AdoMet in order to get the binding sites available in DNA methyltransferase [3]. This compilation leads to DNA hypomethylation resulting in epigenetic programming [4]. A genome-wide study conducted on human fetal cord blood stated the possibility of homocysteine concentration to affect fetal genome but the effect of hyperhomocysteinemia in developing fetus isn't well established and needs to be further explored [5]. It is hypothesized that reprogramming of DNA methylation during embryogenesis cause impaired DNA methylation which plays a significant role in etiology of offspring malformations. Besides, these abnormalities hyperhomocysteinemic condition in mother, gene mutations in the enzyme of "1-C" cycle and decreased methyl levels also have significant roles to play in increasing occurrence of congenital disorders such as Down's syndrome, congenital heart defect, non-syndromic oral clefts, and neural tube defects [4].

Homocysteine is found to disturb the integrity of the blood-brain barrier in a mice model of hyperhomocysteinemia [6]. Although the evidence for homocysteine crossing the blood-brain barrier and effect of hyperhomocysteinemic renal patients on the brain are not satisfactory still, some recent affirmations have proposed that most probably the homocysteine exchange among plasma and brain takes place through bi-directional cellular transporters [7].

The rise in homocysteine levels in the brain and cerebrospinal fluid is associated with many neurological disorders. The rise in homocysteine levels in cerebrospinal fluid and serum runs parallel but the rise in homocysteine levels in serum

is 20 to 100 folds higher than homocysteine levels in cerebrospinal fluid [7]. The neurotoxic effect of methotrexate can be understood by folate depletion and/or increase in homocysteine concentration in the brain because the antifolate treatment causes a fall in folate and S-adenosyl methionine concentrations that leads to rise in homocysteine levels in the cerebrospinal fluid sample [7,8]. The condition of acute hyperhomocysteinemia in children with CBS deficiency can be examined by an around 10-fold rise in homocysteine concentration in cerebrospinal fluid [9].

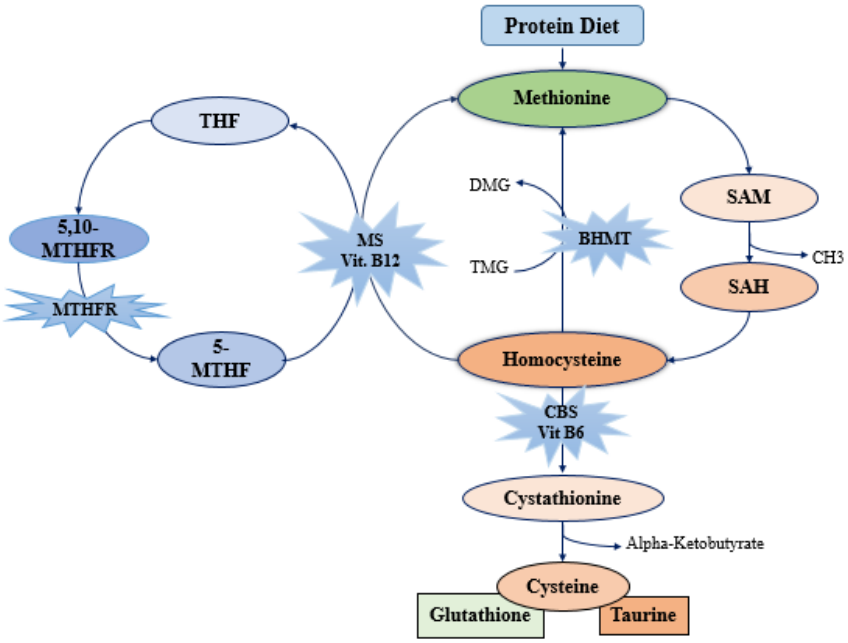

Figure 1 Metabolic pathway of homocysteine

Most of the neurodegenerative diseases namely Alzheimer's disease, Parkinson's disease, and Huntington's disease are age-related and characterized by cognitive and/or motor impairment. These diseases deteriorate with the passage of time, ruin the quality of life, have hiking medical expenses, and ultimately leads to death. Such diseases take a dig at a population of middle-aged to elderly creating burden for the individual as well as society and the healthcare system [10].

The role of hyperhomocysteinemia is discovered in many physiologic conditions but there is lacuna of knowledge when considering neurologic disorder. This review article is a piece of work that reviews the current literature for the link between hyperhomocysteinemia and neurologic disorders namely Alzheimer's disease (AD), Multiple sclerosis (MS), Stroke, Parkinson's disease (PD), and epilepsy [2].

Hyperhomocysteinemia and Alzheimer's disease

Alzheimer's disease is characterized by memory loss or mild cognitive impairments (MCI) of normal age with early dementia. Patients of MCI can perform their routine activities smoothly but with some noticeable memory fluctuations or some other sought of cognitive disturbances. MCI could be amnestic and non-amnestic but both of them fail to be diagnosed for dementia. MCI could be marked as an outset of dementia due to the fact that patients with MCI are found more prone to dementia than normal cognitive patients.

Clinical data reports suggest that hyperhomocysteinemia is an independent risk factor in transforming a healthy cognitive person to dementia in both normal elderly persons as well as persons suffering from Alzheimer's disease [11]. Hyperhomocysteinemia is a condition developed in healthy individuals with or without MCI. A relationship established between learning and hippocampal function and hyperhomocysteinemia suggests that hyperhomocysteinemia degrades cognitive functions in both healthy controls and MCI patients by causing brain atrophy in patients with MCI [2,12].

Another study shows a link between homocysteine, hippocampal plasticity, and synaptic transmission indicating learning and memory shortcomings [13]. The neurotoxicity caused by homocysteine could be explained by the

auto-oxidation of homocysteine that leads to the formation of reactive oxygen species which becomes the cause for neuroinflammation and apoptosis [4,14] (Figure 2). Hyperhomocysteinemia is reported to alter structure and function of cerebral blood vessels by oxidative stress and endothelial dysfunctions that lead to perfusion impairment followed by neuronal disturbances and marked to be as risk factors in the pathogenesis of vascular dementia and Alzheimer's disease [15].

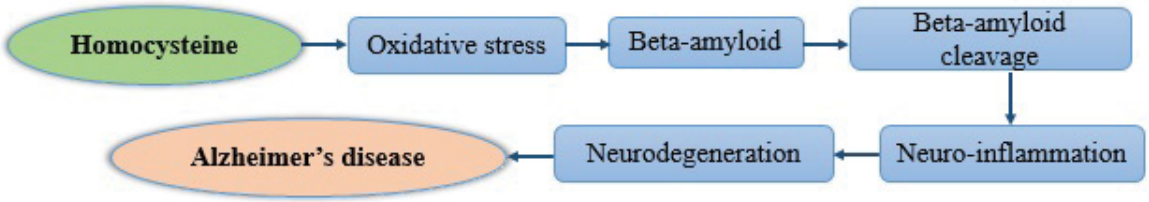

Figure 2 Link of Hcy with Alzheimer's disease

The relation between hyperhomocysteinemia and dementia has gathered a lot of interest in determining the mechanism associated with it. It is believed that it acts by being an excitatory neurotransmitter which competes with inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Additionally, it inhibits GABA-A/B receptors by inducing microvascular permeability which then increases redox stress, which further activates disintegrin and metalloproteinase, terminating tissue inhibitors of metalloproteinase. This disturbs the blood-brain barrier matrix leading to vascular dementia [16].

Zhang, et al., concluded that rises in plasma homocysteine levels possibly induce acquisition of amyloid-beta peptides and also increase Alzheimer's like tau phosphorylation in the rat. It was also found that homocysteine made neurons prone to amyloid-beta toxicity and in hippocampal neurons, it tarnishes the process of DNA repair [17].

Hyperhomocysteinemia and Stroke

The leading cause for adult disability and the second leading cause for death worldwide is a stroke. Stroke is either ischemic or hemorrhagic disturbing the blood flow to part of the brain by rupturing blood vessels. Clinical studies have proven hyperhomocysteinemia to be an indicator of stroke and stroke-related thrombophilia. An expeditiously accumulating relationship between hyperhomocysteinemia and thrombosis via the mechanism of attenuated anticoagulant processes, increased in thrombin generation, impaired enzyme breakdown, and attenuated anticoagulant processes [18].

In patients of hyperhomocysteinemia with homozygous CBS deficiency, were found to have 8-iso-prostaglandin f 2α, a marker for oxidative stress indicating towards high lipid peroxidation due to platelet activation [19]. Hyperhomocysteinemia also includes ocular damages; cases have been reported of redundancy of non-arteritis anterior ischemic optic neuropathy along with CBS deficiency that causes for retinal embolism due to craniocervical arterial dissection [2]. In a context, oxidative stress and impaired fibrinolytic potential in experimentally induced hyperhomocysteinemia suggested that an elevated level of Hcy significantly increase cell neurodegeneration in rat cortex and hippocampus. Hyperhomocysteinemia along with ischemic preconditioning affects intracellular signaling in ischemia-induced neurodegeneration [20].

In ischemic stroke patients with no internal carotid arterial stent-occlusion (ICS), a relationship in the amount of rise of plasma homocysteine levels and pulsatility index in all intracranial arteries came into observation [21]. The ischemic stroke patients with ICS were found to show higher homocysteine levels than those who do not have ICS. Patients with homocysteine level of more than 14.0 μmol/L are found to be at the brink of progression of aortic arch atheroma which is a risk factor associated with recurrence of vascular events in stroke patients and transient ischemic attacks [22]. These studies bring to a conclusion that hyperhomocysteinemia is a mediator for aortic plaque development.

Hyperhomocysteinemia and Parkinson's disease

Parkinson's disease is a neurodegenerative disorder marked by deprivation of neurons in the region of *Substantia nigra* pars compacta with simultaneous dopamine loss from striatum resulting in motor imbalance. The etiology of Parkinson's is not properly established but congenital, environmental and adapted lifestyle is considered as some of

the factors responsible for Parkinson's disease. Clinical studies have shown that hyperhomocysteinemia was observed in patients of Parkinson's disease that may also have an involvement in the pathogenesis of Parkinson's disease [2].

Homocysteine can activate microglia and astrocytes that trigger an inflammatory response which causes neuronal death [23]. In patients of Parkinson's disease, the region of the *Substantia nigra* is found to be inflammation and inhibition of this inflammation has proved to be neuroprotective in Parkinson's disease model. The activation of microglia and astrocytes release NO which shows detrimental effects on neurons resulting in neurodegeneration [24]. The NO release can be determined by following MPTP or 6-hydroxydopamine (6-OHDA) model in rodents and comparing the neuronal death when only 6-OHDA is administered and when it is co-administered with a NO scavenger [25].

The mitochondrion is a site for studying the pathogenesis of various neurodegenerative disorders including Parkinson's disease. By the help of electron microscopy, it was discovered that homocysteine cause mitochondria to swell which is inhibited by binding of cyclosporin a to the mitochondrial matrix protein, Cyclophilin D and thus blocks the calcium-dependent formation of mitochondrial permeability transition (MPT) [26]. This study directly links homocysteine with mitochondrial disruption ultimately leading to neuronal loss in Parkinson's disease.

The most prevailing treatment for Parkinson's disease i.e., levodopa has a complication with homocysteine levels. It induces hyperhomocysteinemia due to its methylation via catechol-O-methyltransferase (COMT). This complication can be cured by treating patients with entacapone as it is a COMT enzyme inhibitor. However, even after all these studies considering hyperhomocysteinemia as an independent risk factor for Parkinson's disease still needs to be further studied for proving the assumption [27].

The confusion lies because the pathways linking homocysteine with neuronal cell death merge at a point i.e., oxidative stress, which can both cause hyperhomocysteinemia and as well as be an outcome of hyperhomocysteinemia making it difficult to decide which occurs first (Figure 3). In this confusing relationship between hyperhomocysteinemia and Parkinson's disease animal models have helped in conforming that antioxidants reduce the effects of homocysteine and are also found lowering the effect of bone loss in Parkinson's disease [28,29].

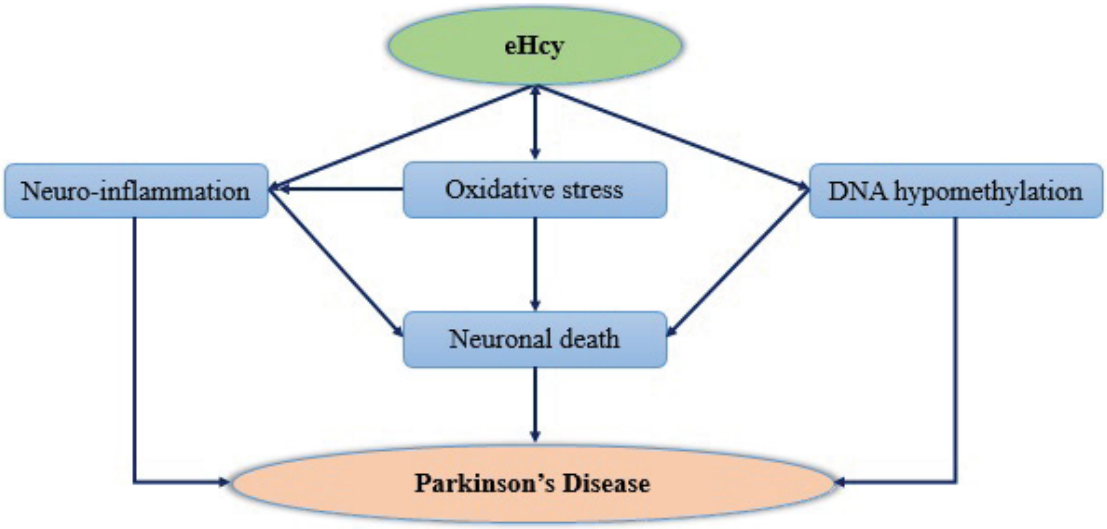

Figure 3 Link of Hcy with Parkinson's disease

Hyperhomocysteinemia and Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory disease intervened by autoimmune demyelination of neurons of the central nervous system. Patients with multiple sclerosis are known to have hyperhomocysteinemia but with no link to either immune activation or oxidative stress or any kind of vitamin deficiency [30]. It can be hypotheses that Hcy increases the production of chemokines via the underlying mechanism of PKC, CaM, MAPK, and NF-□B that leads to the pathogenesis of MS [31-33].

The possible mechanism underlying with multiple sclerosis and hyperhomocysteinemia is believed to be the

hyperhomocysteinemia induced excitotoxicity that adjusts the methionine availability which in turn intrudes with methyl donors in biochemical reactions. This creates the condition of hypomethylation of myelin basic protein resulting in reduced stability of myelin sheath and higher susceptibility to depletion [2].

Hyperhomocysteinemia and the Cytoskeleton of Neural Cells

Experimental studies have shown that hyperhomocysteinemia induced vulnerability of hippocampal cytoskeleton in brain slices. The outcome has proved that misregulated phosphorylation was noticed in postnatal on day 17, which is associated with the intermediate factors in the hippocampal region of the brain. Hyperhomocysteinemia alters the signaling mechanism of PPA, PP2A, and PP2B-mediated hypophosphorylation of neurofilament subunits (NF) and glial fibrillary acidic protein (GFAP) in hippocampal slices of 17-day old rats [34].

Hyperhomocysteinemia and Impaired Pregnancy

Under homeostatic conditions, homocysteine levels get lower during normal pregnancy. But complications during pregnancy leads to hyperhomocysteinemic conditions whose outcome is new-borns are born with neural-tube defects (NTDs) [35]. This defect is produced in the baby during the first month of pregnancy and most commonly occurring forms of neural-tube defects are spina bifida and anencephaly. In fetal suffering from spina bifida their spinal column does not close completely and while in case of anencephaly majority of brain and skull region remains underdeveloped and such births are either still-birth or die after birth.

Studies have revealed that hyperhomocysteinemia increases the risk of preeclampsia and miscarriages due to placental vascular endothelium dysfunction [36,37]. When comparing homocysteine level of pregnant women diagnosed with preeclampsia to that of control it was observed that plasma concentration of homocysteine in preeclamptic women was 16.39 μmol/L and in control, it was 9.45 μmol/L at $p \leq 0.001$ [38].

The next related issue comes to be putative teratogenic effects of elevated homocysteine levels. The pregnant women, when on anticonvulsant therapy during their first trimester gain the risk of major congenital malformations in their newborns. Although the mechanism behind teratogenicity in folate deficiency remains unsure but is most probably linked to elevated homocysteine levels. In pregnancies complicated by neural tube defects, the homocysteine levels in amniotic fluid were found quite high. After such scrutinizes, American Academy of Neurology came with a recommendation to all women with childbearing potential to consume a minimum of 0.4 mg folic acid per day if they were on anticonvulsant therapy. Whether this recommendation is effective in lowering homocysteine levels or incidences of neural tube defects in epileptic women is still to be explored. The necessity of cyanocobalamin and pyridoxine hydrochloride supplementation for this population remains uncertain [39].

Hyperhomocysteinemia and Epilepsy

Epilepsy is a neuronal disorder occurring due to an aberrant firing of cerebral cortical neurons resulting in repetitive and unconscionable seizures. The observable signs of seizures could be convulsions, hypertonic and stereotyped movements, amendments in perceptions and sensations, and state of unconsciousness.

Patients of epilepsy are seen to have hyperhomocysteinemia but besides epilepsy, there could also be some other prevailing factors such as adverse effect produced due to long-term use of anti-epileptic drugs (carbamazepine, gabapentin, phenytoin, primidone, valproate, and oxcarbazepine) particularly in epileptic patients which could be responsible for producing hyperhomocysteinemic condition [40]. Gorgone, et al., found a higher rate of brain atrophy in MRI reports of 58 epilepsy patients with hyperhomocysteinemia together with being on antiepileptic drugs. From these observations, he has drawn a conclusion that both hyperhomocysteinemia and polypharmacy confers to brain atrophy in patients with epilepsy [41].

In pediatric epilepsy cases with homocystinuria, it is observed that higher levels of homocysteic acid and homocysteine sulfinic acid show excitotoxicity through both NMDA (N-methyl-D-aspartate) and non-NMDA receptors. Also, hyperhomocysteinemia ceases the activity of glutamate decarboxylase and interrupts metabolism of glutamate-glutamine [42].

The fact that high doses of homocysteine when administered systemically in animals produce seizures, is highly utilized in experimental models of epilepsy. Another fact that is discovered is that around 20% of patients with homozygous CBS deficiency experience seizures which when paired with high plasma homocysteine concentrations

of generally 50-200 µmol/L could turn into epilepsy. However, the lower plasma homocysteine levels which range from 15-20 µmol/L does lead patients to epilepsy is not yet stated [39].

Hyperhomocysteinemia and Peripheral Neuritis

Peripheral neuritis is a disease of elderly people which has varying symptoms of sensory, motor and autonomic functional imbalances depending upon the nerve fibers involved. The various etiologies found till date includes metabolic disorders, infections, inflammation, malnutrition, auto-immune mediated, inherited factors and toxicities of specific drugs and radiations. Clinical studies stated that hyperhomocysteinemia increases the risk of peripheral neuropathy in diabetic patients and worsen the pre-existing condition of diabetic neuropathy in patients of peripheral neuritis [43].

Earlier studies on pig model showed an elevation of adenosylhomocysteine (AdoHcy) level in neural tissues in methyl deficit condition and proposed that this raised level of AdoHcy causes peripheral neuropathy that is potentially treatable [2,44].

Hyperhomocysteinemia and Neuronal Cell Death

The plasma homocysteine level ranging across 15-100 µm give rise to the condition of mild to moderate hyperhomocysteinemia which has been proven as a risk factor for various neurodegenerative disorders. While the hyperhomocysteinemic condition prevails in the body the raised levels of homocysteine concentration in the brain could be a result of either cellular metabolism within brain or diffusion and carrier/receptor-mediated transport across blood-brain barrier [6].

Poddar, et al., studied the activation of the extracellular-signal regulated mitogen-activated protein (ERK MAP) kinase regulated by NMDA receptor. The ERK MAP pathway was used in the study of homocysteine-dependent neurotoxicity. The study helped to know certain facts regarding homocysteine-dependent neurotoxicity such as cell death induced due to L-homocysteine is regulated via stimulation of NMDA receptors and Ca^{2+} influx which rapidly phosphorylate ERK MAP kinase (Figure 4). The study also suggested that stimulation of ERK MAP kinase pathway is an intermediate step in homocysteine-dependent neurotoxicity mediated by NMDA receptor which also states that this neuronal death can be inhibited by blocking ERK phosphorylation [45].

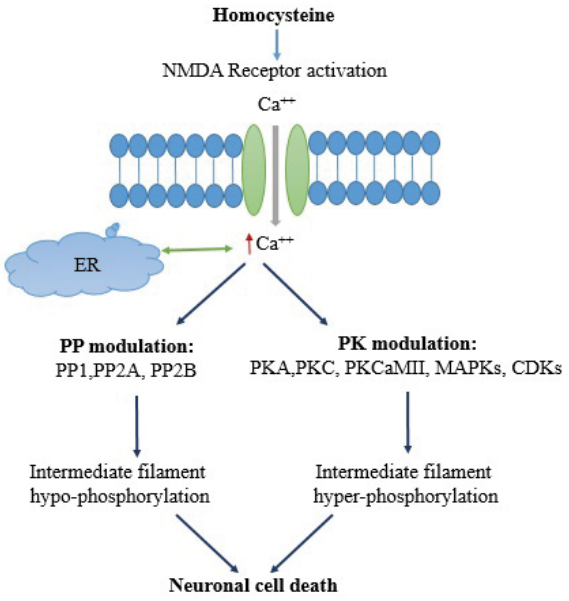

Figure 4 Hyperhomocysteinemia induced neuronal cell death

Hyperhomocysteinemia and Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS), or Motor neuron disease (MND) is associated with the annihilation of neurons

that control voluntary muscles. The symptoms of this disease are stiff muscles, muscle twitching and muscle weakening due to the reduction of muscle size. Zoccolella, et al., reported that homocysteine causes an increase in the expression of PARP and p53 and activity of astrocytes. These proteins serve as modulators of death and survival transcription programmes causing an elevation to motor vulnerability (Figure 5). The plasma concentration of homocysteine also has a positive link with immune activation markers.

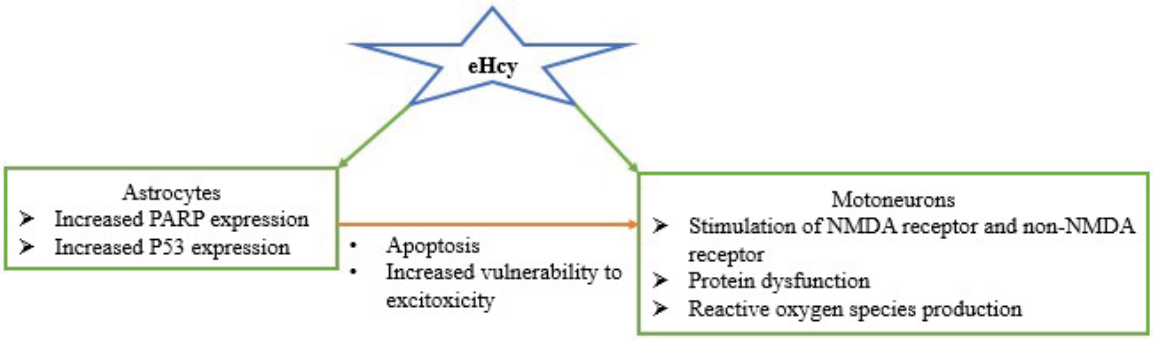

Figure 5 Possible mechanisms of motoneuron damage associated with eHcy

In a pre-symptomatic mouse model of ALS and also in some patients of ALS a condition of inflammation in the areas of motor neuron loss was found which was detected by increased levels of cytokines in serum and cerebrospinal fluid of some ALS patients [46-48].

Table 1 Excitotoxicity and linked models

Authors	Model	Excitotoxicity	References
Dam, et al.	Chronic hypoperfusion induced vascular cognitive impairment in a mouse model	Homocysteine brings down the cortical levels of acetylcholine and disables/spoils reference memory	[49]
Zhang, et al.	Hcy induced Alzheimer's disease in rat	An increase in beta-amyloid due to homocysteine by intensifying the assertion of gamma-secretase and amyloid precursor phosphorylation in brain	[50]
Li, et al.	Diet induce high homocysteinemia in AD transgenic mice	Hcy favors the development of cerebral amyloid angiography via reduction of beta-amyloid clearance and transport within the brain	[51]
Poddar, et al.	Introduction of DL-homocysteine thiolactone to rat embryos tissue culture	Hcy stimulate NMDA receptor, resultant calcium influx leads to phosphorylation of ERK MAP kinase and neuronal cell death	[45]
Choudhury, et al.	Chronic liver disease induced hyperhomocysteinemia	Hcy activates NMDA receptor in the brain, and thereby cause oxidative stress, neuroinflammation, and neuronal loss that lead to hepatic encephalopathy	[52]
Kumar, et al.	HHcy induced vascular dementia in Swiss albino mice	Hcy cause endothelial dysfunction, oxidative stress, cholinergic dysfunction, learning and memory impairments	[53]
Tyagi, et al.	Homocysteine-induced oxidative stress	PAR-4 induced ROS formation increased due to homocysteine by elevation of NADPH oxidase, depletion of thioredoxin expression and decreases no bioavailability	[54]
Zhou, et al.	Homocysteine-induced neurotoxicity	Hcy cause neurodegeneration via modulation of JNK and erk1/2 pathways, resulting in hyperphosphorylation of tau protein	[55]
Gou, et al.	Hyperhomocysteinemia induced Alzheimer-like pathologies in the rat retina	HHcy cause vessel damage with beta-amyloid and tau pathologies in the retina	[56]
Blasko, et al.	A prospective cohort study of individuals aged 75 years	Hcy accelerate the conversion of cognitively healthy to Alzheimer's disease	[57]
Kruman, et al.	Homocysteine treatment in neuronal culture	Activation of PARP degrades neuronal energy to the point of neuronal apoptosis causing DNA damage, all due to homocysteine	[58]

Zoccolella, et al.	Hyperhomocysteinemia in L-dopa treated patients with PD	Hyperhomocysteinemia linked to L-dopa for cognitive impairment and dementia while in the course of Parkinson's disease	[59]
Duan, et al.	MPTP induced Parkinson's Disease mice gets sensitized due to folate deficiency in the diet	Dopamine decrease and motor dysfunction worsen in MPTP induced Parkinson's disease model due to homocysteine	[60]
Valkovic, et al.	A cross-sectional study	The mean plasma concentration was found higher in the subjects on the treatment of levodopa	[27]
Iacobazzi, et al.	CBS and MTHFR gene abnormalities	Hcy causes neural tube closure defects, heart defects, cleft lip/ palate, down syndrome, and multi-system abnormalities in adults	[3]
Zaccolella, et al.	Hcy levels investigation in ALS patients	Higher median Hcy levels in patients associated with ALS	[46]
Ramsaransing, et al.	Hcy levels investigation in MS patients	eHcy occurs in both being and progressive disease courses of MS seems unrelated to immune activation.	[30]
Loureiro, et al.	Hcy induced cytoskeletal remodeling and production of reactive oxygen species in cultured cortical astrocytes	Hcy (10 and 100 micromoles) treated neurons presented unaltered neurite arborization.	[61]
Mwakikunga, et al.	Hcy treated cultured neural tube explants	Hcy causes more spreading, migration of neural crest cells, and effect on LIM3 suggest the modulation in the signaling of the cytoskeleton	[62]
Şanlıkan, et al.	A case-control study	Elevated levels of Hcy was found in patients with preeclampsia	[63]
Baldelli, et al.	Hcy pre-treatment in the pilocarpine model of status epilepticus	eHcy enhance seizure activity and neurodegeneration in pilocarpine-treated rats	[64]
Apeland, et al.	Own matched control based study	Drugs such as phenytoin, primodine, and phenobarbital belonging to anti-epileptics category share a link with high plasma homocysteine and low folate levels in adult patients.	[65]
Shandal., et al.	eHcy induced peripheral neuropathy in thirty subjects	Results seven subjects had pain in lower extremities, and 10 subjects had tingling in feet	[66]

CONCLUSION

The imbalance homocysteine levels have a lot to do with various cognitive diseases. Disruption in homocysteine metabolism become a cause for redox impairment leading to the formation of reactive oxygen and nitrogen species that again become the base for the pathogenesis of various neurological disorders.

In Alzheimer's and dementia homocysteine is known to amplify amyloid beta deposition, altered presenilin functions and at times is found to restrain hyperphosphorylation of tau protein. Next to carotid atherosclerosis or white matter lesion, raised levels of homocysteine are an early marker for the disease. The relationship between hyperhomocysteinemia and cognitive impairment through amyloid deposition and white matter hyperintensities is clinically proven.

Hyperhomocysteinemia has also become a subject of debate when considering it as a risk factor for neural tube defects (NTD) and non-communicable diseases such as type 2 diabetes and cancer. This alteration in plasma homocysteine levels are known to be an outcome of lifestyles, environmental subjection, hormonal imbalances, disease severity and could be even an iatrogenic outcome. On a concluding note, it could be noted that a mere elevation in homocysteine level could be a point of consideration in the development of seizures and neurodegenerative disorders such as multiple sclerosis, Parkinson's disease, and amyotrophic lateral sclerosis.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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