International Journal of Scientific Research in Science and Technology
Print ISSN: 2395-6011 | Online ISSN: 2395-602X (www.ijsrst.com)
doi : https://doi.org/10.32628/IJSRST229137

Ageing, Neurodegeneration and Parkinson's Disease

Mr. Bishal G C
School of Pharmacy, Sharda University, India

Article Info
Volume 9, Issue 2
Page Number : 61-70

Publication Issue
March-April-2022

Article History
Accepted : 01 March 2022
Published : 15 March 2022

ABSTRACT

For the human development aging is one of the important aspect among which on cellular processes and functions are predispose to neurodegeneration and synthetic changes in the body are involved in the pathogenesis of Parkinson's. The accumulation of the cellular development and their function leads to the progression of Parkinson's. The formation of ROS, generation of oxidative stress, disruptions in inflammatory pathways like COX, LOX, formation of lewy bodies, protein degradation, genetic mutations, mitochondrial depletion and several other pathways involved in the pathogenies. These may be due to age related decline in acetylcholine and dopamine levels. On medical findings from survey it's been discovered Parkinson's is age associated ailment and quite a times irreversible yet curable on early stages and can be treated with dopamine and acetylcholine analogues, where levodopa and carbidopa is considered to be the drug of choice at different doses for the inhibiting progression of Parkinson's.

Keywords : Neurodegenerative disease, Genome instability, Life expectancy, Ageing, Parkinson's disease, Alzheimer disease

1. INTRODUCTION

In living creature, "ageing" usually refers to a sequence of time-dependent bodily and anatomical adjustments that lessen Physiological reserve and useful capacity. Ageing happens at different rates in numerous species, and inter-individual variations exist within a species and in the different tissues of an individual. The principal motive of getting older in most character is their lifestyle, own circle of relatives genes and the outcomes of the environment. Although mind cells are especially liable to the collected outcomes of getting older. An important modification throughout ageing is that the loss of irreplaceable cells, most perceptibly within the brain, heart, and skeletal muscles. We all age, our brains age, but only a few humans broaden neurodegenerative diseases. Neurodegenerative disorder is regression and progressive deterioration of neurological characteristic with lack of speech, vision, hearing, or locomotion, frequently related to seizures feeding difficulties, and impairment of mind. (Shubhankar, M., and P. M. Ajit,2018). The neurodegenerative diseases are Parkinson's disease (PD), Alzheimer disease (AD), prion disease, Motor neuron disease (MND), Huntington's disease (HD) , Spinocerebellar ataxia (SAA) ,Spinal muscular atrophy (SMA). Alzheimer disease is a progressive disease that destroy memory and other important mental functions

and cause by abnormal build build-up of protein in and around brain cell and also by increase in acetylcholine (ACH). Parkinson‘s disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopamine (Dawson TM, 2006). In addition to dopaminergic neuropathology, there is dysfunction in cholinergic, serotonergic, glutamatergic and noradrenergic pathways (Charvin, D., Medori, R., Hauser, R. et al., 2018). PD is classified as a synucleinopathy, as α-synuclein, a presynaptic neuronal protein, is a major constituent of Lewy bodies, which are a pathological hallmark of PD (Charvin, D., Medori, R., Hauser, R. et al., 2018). Interestingly, α-synuclein has a completely unique significance in the aetiology of PD as it seems to hyperlink familial and sporadic kinds of the disease. The presence of aggregates in patient brains suggests that the proteostasis of α-synuclein is disturbed in PD (Charvin, D., Medori, R., Hauser, R. et al., 2018). Indeed, α-synuclein exists in various conformations in a dynamic equilibrium that is modulated by many factors, including oxidative stress, post-translational modifications and concentrations of fatty acids, phospholipids and metal ions, and a tight balance of these factors controls the levels and aggregation of α-synuclein (Charvin, D., Medori, R., Hauser, R. et al., 2018).

Parkinson’s disease (PD) is the second most common neurodegenerative disorder in adults over the age of 60 years. According to the Global Burden of Disease study (2018), the worldwide burden of PD has more than doubled over the past two decades from 2.5 million patients in 1990–6.1 million patients in 2016. India is home to nearly 0.58 million persons living with PD as estimated in 2016, with an expected increase by 19% by 2050 (united nation population India). Recent study (2020) of International Parkinson and Movement Disorder society estimated that 9.4M population live with PD and Country-specific number include; US (930k) , Japan (344k) ,Germany (266k) , France (157k) , Italy (149k) ,UK (142k) , Spain (120k) .According to Parkinson‘s news today an estimated 4 percent of people with Parkinson‘s disease are diagnosed before the age 50 . Men are 1.5 times more likely to have have Parkinson‘s than women.

Many age-associated neurodegenerative sicknesses are characterized through accumulation of disease-unique misfolded proteins in the central nervous system. These include β-amyloid peptides and tau/phosphorylated tau proteins in AD, α-synuclein in PD, superoxide dismutase in amyotrophic lateral sclerosis, and mutant huntingtin in Huntington’s diseases (Hung, Chia-Wei, 2010). The relationship between age and protein misfolding is not yet clear. It can be associated with cellular changes that arise all through ageing. For example, cells reduce and the best manipulate of protein synthesis declines with ageing. This might also additionally reason or make contributions to the formation of misfolded protein aggregates and in the end cause disease. In a small number of the population, aging neurodegeneration is accelerated by individual (e.g. brain injury), environmental factors (e.g. toxins) and genetic factors (e.g. alphasinuclein gene mutations) in order to reach the critical threshold of clinical symptoms throughout lifetime (Müller, W. E., Eckert, A., Reddy, P. H., eds., 2020). Thus, neurodegeneration in Parkinson's it appears to represent the common ultimate pathway of "normal brain aging" and all other risk factors, including genetics and the accumulation of the neurotoxic protein alpha-synuclein (Müller, W. E., Eckert, A., Reddy, P. H., eds., 2020). Ageing affects several cellular processes that incline to neurodegeneration, and age-associated modification in cellular perform predispose to the pathological process of PD. The build up of age-associated somatic harm combined with a failure of compensatory mechanisms. The etiology underlying the improvement of Parkinson's remains unclear. So far, around 18 genes have been recognized as the genetic causes for familiar Parkinson's disease, which provide crucial information about the pathogenesis of the disease. Recently,

accumulating genetic discoveries have discovered the association among vesicle trafficking and parkinson's disease. The disruption of cell vesicle traffic leads to impaired breakdown of certain proteins and also leads to abnormal protein aggregation, which has a toxic effect on neurons. Rab GTPases (Rabs) carry out the primary features in intracellular trafficking events. Moreover, a sequence of new research have found out that the certain rabs are involved in modulation of α-synuclein. The alteration of these proteins has been reported to be one of the rare causes of early hereditary PD. These new findings provide new insight into the molecular pathogenesis of PD.

2. Mechanism of ageing

Genome instability

Genome instability is define as the process prone to genomic changes with high frequency of mutation to chromosomal rearrangement. It can be divided into two types- chromosomal instability (CIN) and micro- and mini- satellite instability (MIN). Chromosomal instability refers to changes in chromosomes structure and number that lead to chromosomes gain or loss. It is cause by the failure of mitotic chromosomes transmission or spindle mitotic check point. Micro- and mini satellite instability leads to repetitive DNA expansion and contraction and occur by replication slippage, mismatch repair impairment, homologous recombination etc. During cell cell division genomic instability is associated with failure of parental cells to accurately duplicate the genome and precisely distributed the genomic material among the daughter cells. Genetic instability can also have a specialized role in the generation of variability in developmentally regulated process, such as immunoglobulin (Ig) diversification.

According to the figure 1, DNA damage occurs due to exogenous threats (physical, chemical, biological) and endogenous threats (replication error, spontaneous hydrolytic reactions, reactive oxygen species). When DNA damage erroneous DNA repair or replication occurs and results in to DNA mutation. After DNA mutation neoplastic transformation, cellular degeneration and functional decay occurs which ultimately results in to cancer, degenerative disease, ageing etc.

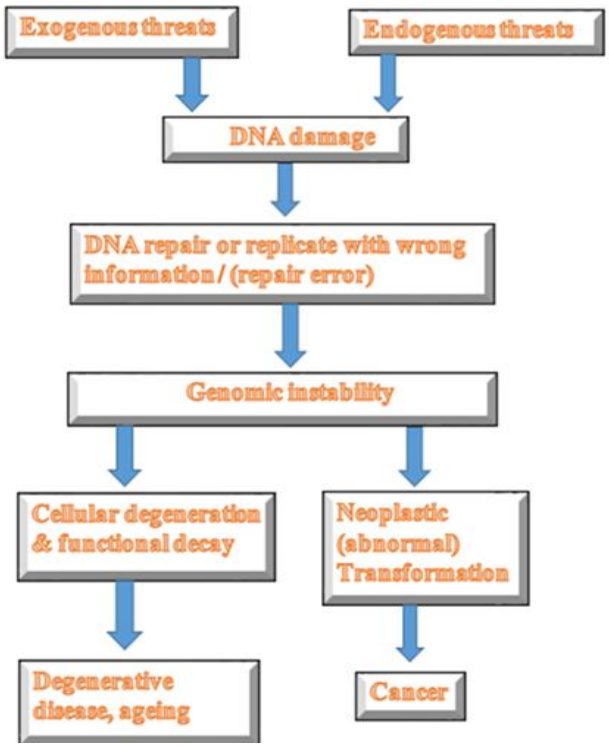

Figure 1. Mutation, Ageing & DNA damage

3. Role of genetical and environmental factor in ageing

Structural and function throughout life is maintain organism by genes. Healthy ageing and longevity in humans are controlled by the combination of genetics and non-genetics factors. Family studies shows that 25% of variation in human longevity is due to genetics factors. Genetics is a powerful tool for identifying the mechanisms of ageing. Large-scale genome-wide association studies have recently identified many loci that influence key human ageing traits, including life span. Multi-trait loci have been linked with serval age-related disease, suggesting shared ageing influences. Vertebrate possesses specialized system so the genetics of ageing is more complex in vertebrate. According to researches gene sirtuin 6 (SIRT6) is responsible for more efficient DNA repair in species with longer life spans. Genetic disease like progeria also known as Hutchinsons-Gilford progeria syndrome (HGPS) or the

Benjamin buttom disease cause child's body ageing rapidly. Progeria disease is cause by the LMNA gene. This disease affects human of all gender and races equally. Almost all children with Hutchinsons-Gilford progeria syndrome (HGPS) don't live past age 13. Symptoms of progeria are a high pitched voice, hair loss including eyelashes and eyebrow, slow height and weight growth, a bigger head etc.

Temperature, food, pollutants, population density, sound, light and parasite are the environmental factors. This environmental factors either damage cellular macro-molecules or interfere with there repair. Environmental factors are responsible for the ageing process. Environmental factor could interact with genetic factor to regulate ageing and mutation that extend life span in certain condition could have different effect when condition changes. For example growth hormone (GH) deficiency increase life span under basal condition but it decrease lifespan when combine rapamycin.

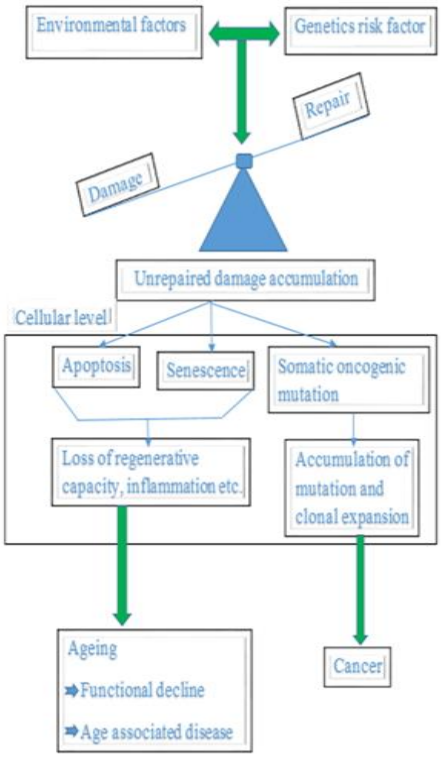

Figure 2. Major influences and mechanism of ageing

4. Theories of ageing

There is vast difference between the lifespan of animal species. Lifespan for mayflies is less than one day and for ocean quahong is more than 400 years. This enormous difference in their lifespan is due to their different abilities to adapt to the surrounding environment and response to stress, both of which are likely genetically encoded. The most globally accepted theories are given below.

Mutation accumulation theory

This theory was proposed by Peter Medawar in 1952. This theory suggest that ageing is a by-product of accumulation deleterious mutation over a time. Due to the illness leading to the death or stochastic risk of accident there is a decreasing probability of reaching more advance age. Deleterious germ line mutation are selected against early in the life when chance of survival and reproduction is high but are hidden from the natural selection (shadow area in the figure 3) at old age.

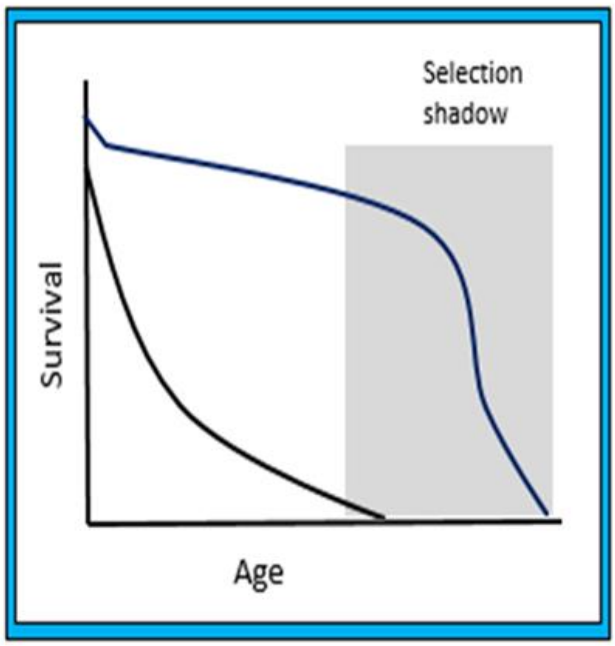

Figure 3. Accumulation of deleterious mutation can occur in the selection shadow because after reproduction, natural selection is week.

Antagonistic pleiotropy theory

This theory was 1st proposed by George Williams in 1957. This theory argues that some mutations selected because they are beneficial to early fitness becomes harmful in late life, causing ageing. Cell senescence pathway may provide may provide example in this theory. During normal mammalian development programmed senescence protects against cancer and promotes wound healing at younger age but contributes degenerative chronic disease at older age.

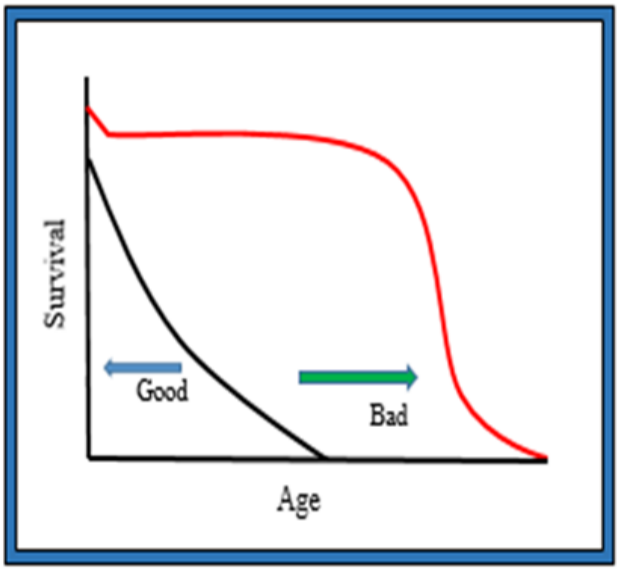

Figure 4. Unlike the mutation accumulation theory the gene suggested to be involve with the ageing phenotype in the pleiotropy theory are beneficial in early life

Disposable soma theory

This theory was formulated by British biologist Thomas Kirkwood in 1977. This theory states that given the availability of limited resources, ageing arises from the evolutionary trade-off between the growth and reproduction, on the one hand, and repair mechanism on other. Disposable soma theory is consistent with the proof that long-lived species such as human evolved by developing more sophisticated and effective, although not unlimited. For examples comparative studies have found that the capacity to recycle deteriorated macromolecules and organelles by autophagy correlates with lifespan across species.

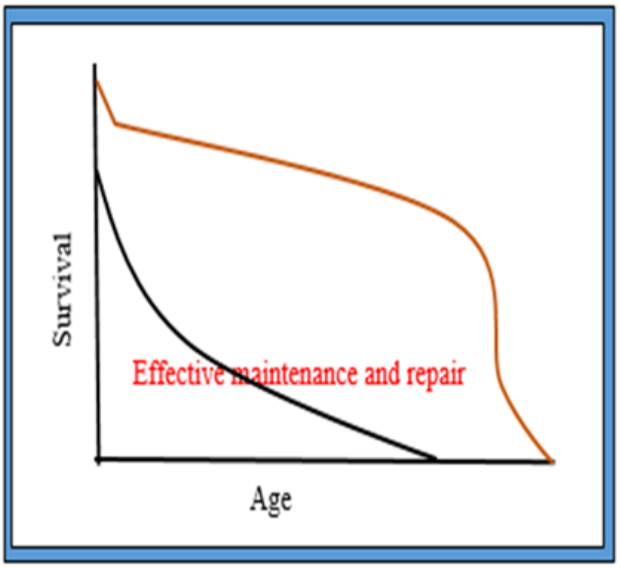

Figure 5. A representation of the disposable soma theory illustrating that effective cellular maintenance is only beneficial while there is a reasonable probability of survival

5. Life expectancy

According to world health organization WHO "Life expectancy is defined as "the average number of years a person is expected to live, based on current mortality rates and the prevalence distribution of health conditions in a population". Worldometer shows that life expectancy in 1950 AD was 47.0 years for both sexes while in 2020 AD life expectancy is 73.2 years for both sexes. In 70 years life expectancy increase by 26.2 years for both sexes. The reason for progress in life expectancy are due to betterment in education, medicine, public health, nutrition, per-capita income, government policies etc. when we compare the life expectancy between male and female we found that female have more high life expectancy than male (from figure 6). Scientist have said that space is because of a mixture of biological and social differences. Men's hormones testosterone is connected to a lower of their immune gadget and threat of

cardiovascular illness as they age. It is likewise connected to unstable behaviour: smoking, consuming alcohol and unhealthy eating habits. If diagnosed, guys are much less probable than girls to comply with doctor advice. Statistics display that guys are much likely to take life-threatening dangers and to die in automobiles accidents, or gun fights.

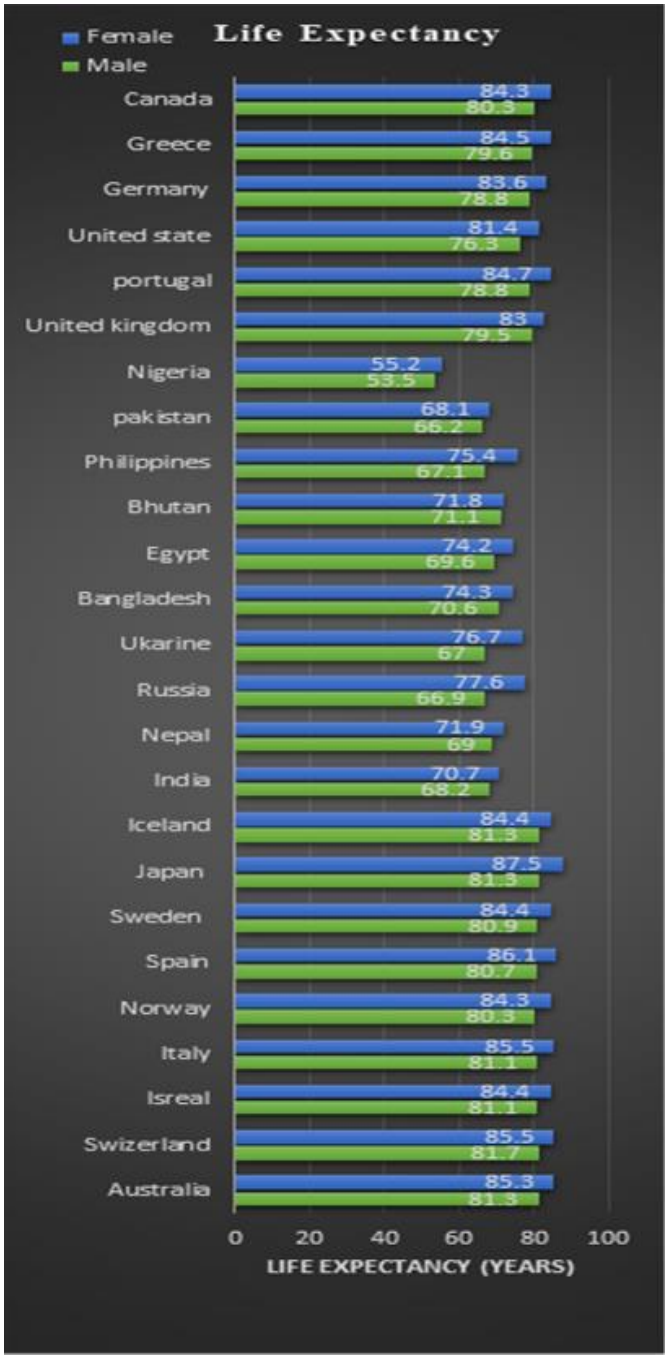

Figure 6. Life expectancy of different countries in 2020

6. Relation between ageing and neurodegeneration

Neurodegeneration is one of the most widespread age-related diseases suggesting a link between neurodegenerative diseases and age-related changes that occur in the microenvironment of the brain such as: genomic instability, changes epigenetics and loss of proteostasis. Although growing old is thought to be a prime danger element for neurodegenerative illnesses. Different types of neurodegenerative disease affect different or same brain region like Parkinson's disease, Huntington disease, Alzheimer's disease, Frontotemporal degeneration affect basal ganglia, Alzheimer's disease, Frontotemporal degeneration, Multiple sclerosis affects thalamus, Frontotemporal dementia, Alzheimer's disease, Tremors, Parkinson's disease, Huntington disease, Amyotrophic lateral sclerosis, Neuro psychiatric disorders affects Cerebral cortex, Frontotemporal lobar degeneration, Parkinson's disease, Huntington disease, Frontotemporal dementia, Amyotrophic lateral sclerosis, Spinocerebellar ataxia affects brain stem, Multiple sclerosis, Multiple systemic atrophy dystonia, Alzheimer's disease, Spinocerebellar ataxia affects cerebellum etc. Figure 6 describes some of the common factors responsible for the onset and progression of neurological disease, and provides a better understanding of the pathophysiology (Behl, T,2021)

Population-based autopsy research of the brains of elderly those who had now no longer been recognized with a neurological disease continuously file the presence of amyloid plaques, neurofibrillary tangles, Lewy bodies, inclusions of TAR DNA-binding protein 43 (TDP-43), synaptic dystrophy, the loss of neurons and the lack of brain volume in most of the brains. (Elobeid,2016). These traits range extensively among individuals, with precise lesions dominating a selected mind or being restrained to precise regions. It isn't acknowledged what reasons those lesions and whether or not or now no longer they're the precursors to neurodegeneration and illness or simply the

manufactured from mind ageing. According to at least one hypothesis, in everyday ageing, macromolecules come to be oxidized and might now no longer be degraded with the aid of using lysosomes. (Brunk, 2002). This outcomes in the greater manufacturing of lysosomal enzymes which is probably moreover now no longer capable of digest the cell material. A famous deposit that outcomes from lysosomal inefficiency is lipofuscin, that's an typical marker of aging for post-mitotic cells. (Brunk, 2002).

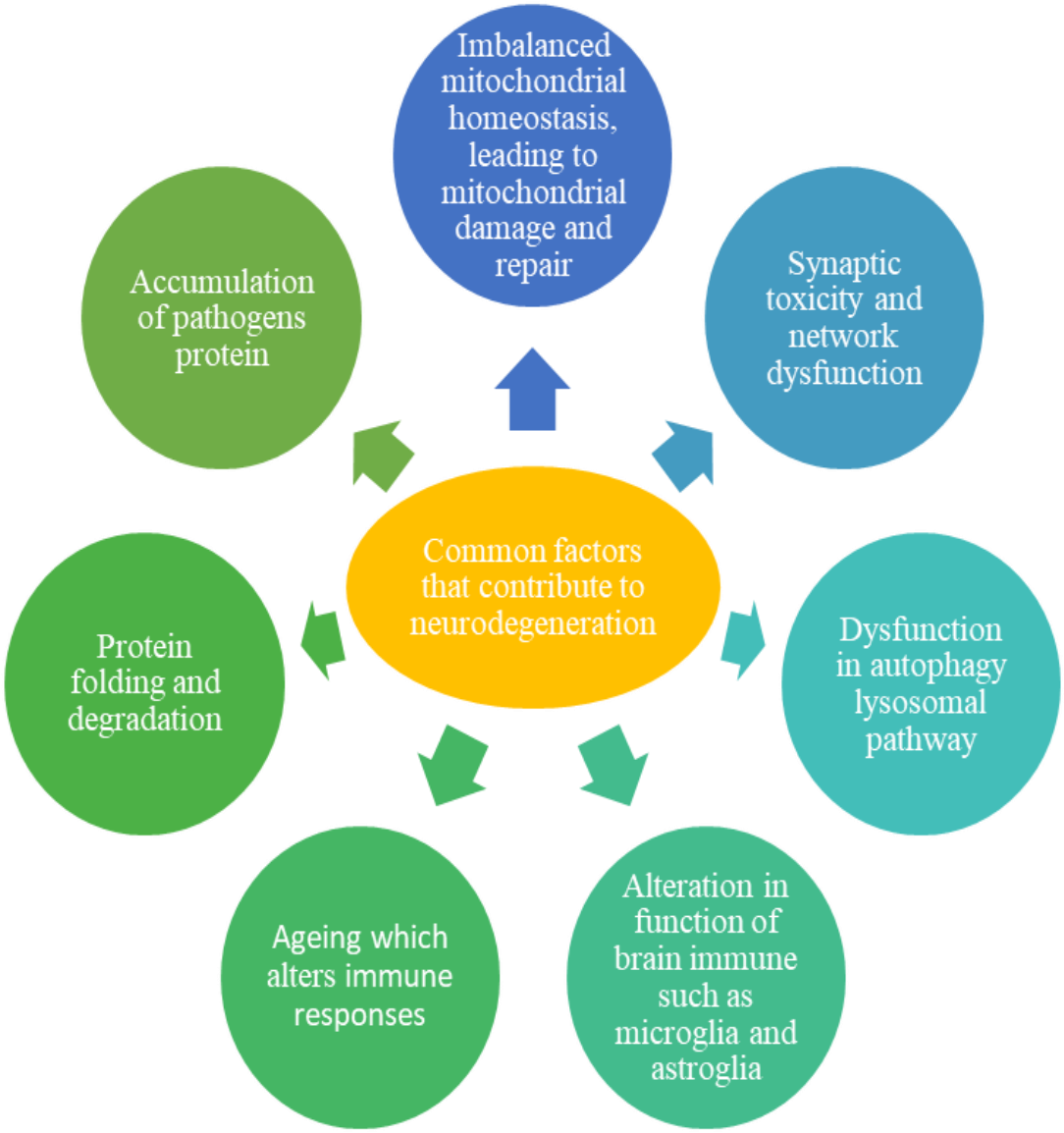

Figure 7. Some of the common factors responsible for initiation / progression of neurological disease.

7. OBSERVATION

Survey was taken from Sharda hospital and guided by Dr. Vikash bhardawaj

QUESTION	ANSWER
What age does Parkinson's disease is usually seen/start?	People usually develop the disease around age 60 or older.
Which gender is seen more with Parkinson's disease?	Parkinson's disease seems to occur more commonly in men than women.
Duration of Parkinson's disease?	In natural conditions, the average duration of Parkinson's disease is 10 years, although with a considerable range.
Life span of Parkinson's disease?	Patients usually begin developing Parkinson's symptoms around age 60 and many live between 10 and 20 years after being diagnosed.
Medicine used and often changed in Parkinson's disease?	A. Levodopa + carbidopa=(lodosyn) B. Dopamine agonist= pramipexole dihydrochloride (mirapex) dose 0.25gm C. Cognition-enhancing medications= acetylcholinestrease inhibitors and memantine / donecept5 (donaprazil hydrochloride) 5mg/day. D. Anti-tremors= Anticholinergics/ benztropine (cogentin) trihexyphenidyl (Artane) dose= 1-2mg/day. E. Antidepressants= citalopram (citapad 20) dose= 20 mg
Complication with Parkinson's disease?	You may experience cognitive problems (dementia) and thinking difficulties, Depression and emotional changes Swallowing problems Chewing and eating problems Sleep problems and sleep disorders Bladder problems Constipation
What symptoms are there usually seen in Parkinson's disease?	Tremor. A tremor, or shaking, usually begins in a limb, often your hand or fingers Slowed movement (bradykinesia) Rigid muscles Impaired posture and balance Loss of automatic movements Speech changes Writing changes Dementia
What are the Common symptoms seen in Parkinson's disease?	Tremor Bradykinesia Stiffness Impair balance and coordination
Any Unusual symptoms seen in Parkinson's disease?	Like classic Parkinson's disease, atypical Parkinsonian disorders cause muscle stiffness,

	tremor, and problems with walking/balance and fine motor coordination. Patients with atypical Parkinsonism often have some degree of difficulty speaking or swallowing, and drooling can be a problem.
Is Parkinson's reversible?	No
What are the mood related symptoms of Parkinson's disease patient?	Depression. Up to half of all Parkinson's disease patients end up dealing with depression, Denial Fatigue, Anxiety, Apathy etc.
Up to what extent we can manage Parkinson's disease?	Parkinson's disease can't be cured, but medications can help control your symptoms, often dramatically. In some more advanced cases, surgery may be advised. Your doctor may also recommend lifestyle changes, especially ongoing aerobic exercise. Some people with Parkinson's are still working 20 years after their diagnosis. Some people who find that their symptoms make work difficult are able to transfer to a different, more manageable job or work part-time. Others are unable to continue in their jobs after a year or two.
What other treatment we can provide other than therapeutic treatments in Parkinson's disease patient?	Tai Chi. This form of exercise promotes balance and coordination, so it stands to reason that it would be beneficial for patients with Parkinson's disease Yoga Massage Therapy Movement Therapies Acupuncture

8. CONCLUSION

The mechanisms of aging and neurodegeneration are complicated and inter-associated. Ageing is the single most important element influencing the scientific presentation and path and development of PD. Normal aging can be related to very moderate parkinsonian signs, while PD has a awesome scientific picture. PD displays a failure of the regular cell compensatory mechanisms in susceptible mind regions, and this vulnerability is expanded with the aid of using a genetic susceptibility acted upon with the aid of using different genetic and environmental elements and most significantly with the aid of using age. The accumulation of age-associated somatic harm blended with a failure of compensatory mechanisms may also cause an expanded occurrence and an acceleration of PD with age. Ageing is, therefore, the primary enhancing element at the phenotypic presentation of PD. PD is an awesome instance of an age-associated disease.

9. ACKNOWLEDGEMENT

I would to like express my special thanks of gratitude to our dean sir Dr. MATHEW GEORGE (Sharda University, school of pharmacy) and our teacher Ms. VAISHALI CHADHA who help me to doing this review paper. Secondly I would also like to thank our

teacher Dr. SHOBHIT SRIVASTAVA who indirectly guided me for completing this review paper.

10. REFERENCES

[1]. Shubhankar, M., and PMAjit"Approach to Neurodegenerative Disease in Children: A Short ReviewProg Asp in Pediatric & Neonat 1 (5)-2018." PAPNMSID 121http://dx.doi.org/10.32474/PAPN.2018.01.000121

[2]. Dawson TMParkin and defective ubiquitination in Parkinson's diseaseJ Neural Transm Suppl2006;(70):209-13doi: 10.1007/978-3-211-45295-0_32PMID: 17017531.

[3]. Charvin, D., Medori, R., Hauser, Ret alTherapeutic strategies for Parkinson disease: beyond dopaminergic drugsNat Rev Drug Discov 17, 804–822 (2018)https://doi.org/10.1038/nrd.2018.136

[4]. Hung, Chia-Wei, et al"Ageing and neurodegenerative diseases." Ageing research reviews 9 (2010): S36-S46.

[5]. Müller, WE., Eckert, A., Reddy, PH., edsInterphase Between Aging and Neurodegenerative DiseasesLausanne: Frontiers Media SA(2020) doi: 10.3389/978-2-88963-456-9

[6]. Behl, T.; Makkar, R.; Sehgal, A.; Singh, S.; Sharma, N.; Zengin, G.; Bungau, S.; Andronie-Cioara, F.L.; Munteanu, M.A.; Brisc, M.C.; Uivarosan, D.; Brisc, CCurrent Trends in Neurodegeneration: Cross Talks between Oxidative Stress, Cell Death, and InflammationIntJMolSci2021, 22, 7432https://doi.org/10.3390/ijms22147432

[7]. Elobeid, A., Libard, S., Leino, M., Popova, SN& Alafuzoff, IAltered proteins in the aging brainJNeuropatholExpNeurol75, 316–325 (2016).

[8]. Brunk, UT& Terman, AThe mitochondrial-lysosomal axis theory of aging: accumulation of damaged mitochondria as a result of imperfect autophagocytosisEurJBiochem269, 1996–2002 (2002)

Cite this article as :

Mr. Bishal G C, "Ageing, Neurodegeneration and Parkinson's Disease", International Journal of Scientific Research in Science and Technology (IJSRST), Online ISSN : 2395-602X, Print ISSN : 2395-6011, Volume 9 Issue 2, pp. 61-67, March-April 2022. Available at doi : https://doi.org/10.32628/IJSRST229137
Journal URL : https://ijsrst.com/IJSRST229137