# Chapter 1
# Aging and Neurodegeneration: A Preface


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**Abstract** Aging is an irreversible complex phenomenon bringing disorganized status in one's life with threats toward various diseases. While the basic and prime contributor to aging is deteriorative and degenerative biological processes, environmental, genetic, and lifestyle factors stay as co-equal hands. At the stage of aging, one has to encounter a series of disorientations in life and a myriad of diseases, such as diabetes, cancer, cardiovascular diseases, neurodegenerative disorders, and arthritis, to highlight a few. Owing to their high irreversible nature, neurodegenerative disorders are at the frontline among the age-related health disorders, which in all means are accompanied by social and economic burdens. Lack of effective treatment strategies paves more gateways for scientific research to explore the bioactive compounds from various natural resources incorporating healthy diet and lifestyle factors. Even though aging is unique and challenging for each individual, more scientific practices are in need to make the period healthy, which in turn provide a fascinating platform for future research.

**Keywords** Aging · Neurodegeneration · Alzheimer's disease · Parkinson's disease · Healthy aging

## Abbreviations

| | |
|---|---|
| AD | Alzheimer's disease |
| ALS | Amyotrophic lateral sclerosis |
| ATP | Adenosine triphosphate |
| DNA | Deoxyribonucleic acid |
| ETC | Electron transport chain |
| FDA | Food and Drug Association |
| HD | Huntington's disease |

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| NMDA | N-methyl-D-aspartate receptor antagonist |
| PD | Parkinson's disease |
| ROS | Reactive oxygen species |
| WHO | World Health Organization |

## 1.1 Introduction

Aging is an inheritable, inevitable complex phenomenon in one's life, which brings an entropy in many ways. Aging is not a stage from which we can escape, but we must definitely encounter it. Even though we struggle to make our aging healthy, the process is highlighted as disease oriented owing to many deteriorative as well as degenerative changes taking place in our body (Rajawat and Bossis 2008). According to the World Health organization, by 2050, the number of people aged 60 years and above is expected to rise to 2 billion, increasing from 900 million in 2015, and the number of people aged above 80 will triple from that of 2015 (WHO Dementia Report. World Health Organization 2019). In parallel, it is also studied that the number of people aged 60 years and older will exceed the number of children below 5 years of age (WHO 2018). Progressive deterioration of bodily functions from cellular to organic level causing complexities with normal physiological phenomena ultimately leads to death. Apart from the biological factors as contributors, aging encompasses a cumulative circumstance elicited from environmental, genetic, and lifestyle elements (Lopez-Otin et al. 2013).

## 1.2 Major Contributors to Aging

Aging is a period up to which most of the people live. Normal aging brings a chain of biological complications: physical and mental disabilities and diseases, psychological declines, and social deprivations (Hodge et al. 2013; Thompson et al. 2017). Among the string of major and minor contributors to aging, selected few processes enmeshed with aging and related disorders, which persist as cellular and molecular criteria behind aging such as genomic instability and telomere aberrations, epigenetic alterations, loss of proteostasis, cellular senescence, mitochondrial dysfunctions, alterations in intercellular communications, and nutritional irregularities (Lopez-Otin et al. 2013) (Fig. 1.1).

Genomic integrity is attributed to both nuclear and mitochondrial DNA and is disturbed by the accumulation of increased assimilation of damaged DNA caused by any of the factors like DNA strand breaks, mismatches in base pairs, and mutations (Jeppesen et al. 2011). Genetic instability is accompanied by an enhanced release of reactive oxygen species (ROS), which gradually cause inflammatory responses, enhance aging, and unlatch the occurrence of diseases such as cancer and neurodegenerative disorders (Hoeijmakers 2009; Moskalev et al. 2012). Telomere attritions like shortening cause cellular senescence, and it has been identified that the defects in

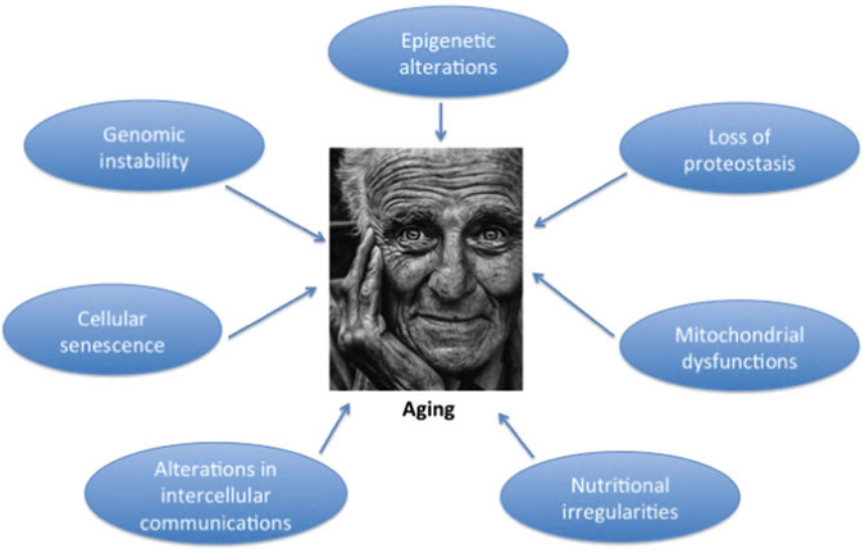


**Fig. 1.1** Schematic representation of major hallmarks of aging (modified from Lopez-Otin et al. 2013)

telomere stimulate aging in mice and humans (Blackburn et al. 2006). Aging is also characterized by epigenetic factors like post-translational modifications of histones, DNA methylation, alterations in chromatin remodeling, etc. (Fraga and Esteller 2007; Bradley-Whitman and Lovell 2013), which can be spontaneous or elicited by external or internal causatives. Another key factor that contributes to aging is loss of proteostasis, equipoised by protein synthesis and degradation. Following aging, the accumulation of damaged proteins due to impairment in ubiquitin or lysosomal pathway results in proteotoxicity. The most prevailing neurodegenerative disorders like Alzheimer's disease (AD) and Parkinson's disease (PD) result from the increased deposition of unfolded/misfolded proteins (Tanaka and Matsuda 2014). Accumulation of senescent cells resulting in cellular senescence is yet another contributor to aging (Lopez-Otin et al. 2013). As age progresses, DNA repair capacity of cells declines resulting in the senescence of cells with high levels of damaged DNA (Madabhushi et al. 2014). The close correlation between mitochondrial dysfunction and aging is highly challenging and has been highly studied. Aging results in inefficient working of electron transport chain (ETC) followed by electron leakage and reduced adenosine triphosphate (ATP) production. This causes elevated ROS levels followed by oxidative stress and subsequent inflammatory responses (Johri and Beal 2012). Impaired intercellular communications and consequential inflammatory responses severely affect the nervous and endocrine systems (Salminen et al. 2012). Irregularities in neurohormonal signaling have an adverse impact on the functional properties of the cells resulting in health disorders. Not least of all, healthy aging and individual longevity are dependent on a restricted diet.

Aging associated with nutritional abnormalities is a highly debated, fascinating field of research. It conveys the relevance of diet and lifestyle factors to prevent premature aging and improve metabolic signaling (Houtkooper et al. 2010).

## 1.3 Aging and Neurodegeneration

As we age, our brains will also age. Aging is not a disease but a potential risk factor for the onset of many diseases. Neurodegeneration is an umbrella term to define the hereditary and sporadic sequence of events determined by the impairment in neuronal functions. Alzheimer's diseases (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) place the top zone of the neurodegenerative disorders (Lakshmi et al. 2018). Even if the abovementioned major hallmarks of aging exist as key players on an even keel, protein abnormalities occur in most of the prevalent neurodegenerative disorders like AD and PD (Fig. 1.2). An overall view of neurodegenerative disorders is often correlated with cognitive disabilities. However, it should also be noted that not all neurodisorders are particularly correlated with the pathological abnormalities related to cognition.

AD, the most prevalent form of dementia, is characterized by the presence of amyloid beta protein (Aβ peptide) and Tau, the major pathological hallmarks, along with defects in presenilin 1 and presenilin 2 (Xia et al. 2018; Bekris et al. 2010). Apart from the above prominent lesions of uncanny accumulation of Aβ peptide and hyperphosphorylated Tau, oxidative stress, mitochondrial dysfunctions, cholinergic

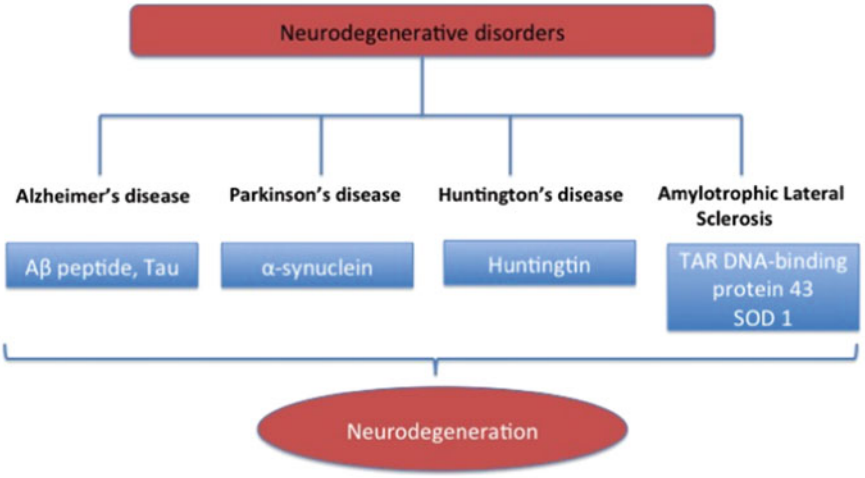


**Fig. 1.2** Neurodegenerative disorders. Alzheimer's disease, Parkinson's disease, Huntington's disease, and amylotrophic lateral sclerosis with their respective causative protein aggregates leading to degeneration of neurons

dysfunctions, and inflammatory responses also join the hub of primary causal agents (Lane et al. 2018). Even though we have drugs, such as cholinesterase inhibitors (tacrine, rivastigmine, donepezil, and galantamine) and N-methyl-D-aspartate (NMDA) receptor antagonists (memantine), approved by Food and Drug Administration (FDA) to combat AD, they can only ameliorate symptoms and cannot reverse the underlying disease processes and that also within limited people and limited ability (Lane et al. 2018; Potyk 2005). Since the major hallmarks of aging mentioned previously are in close harmony with AD, future studies can employ any of them to develop therapeutic interventions. Since current studies are more inclined to nondrug approaches as counteragents of AD, lifestyle interventions and treatments with natural bioactive compounds should be incorporated to treat AD. A decline in sleep is often found in old age people, and sleep deterioration is found in most of the AD patients. Studies have shown the interrelationship between sleep impairment and high Aβ and tau proteins' levels (Liguori et al. 2014). On the other side, exercise and caloric restrictions have been reported to alleviate the AD phenotype (Gunn-Moore et al. 2018). Yet, more studies are in need to confirm the interrelationship between exercise and cognitive enrichment activities to reduce the symptoms of AD (Sexton et al. 2016). The incidence of AD is also associated with insulin and lipid changes/cholesterol levels (Arnold et al. 2018; Foley 2010; Hartmann et al. 2007).

PD is characterized by loss of dopamine-producing neurons in substantia nigra leading to Lewi body formation with aggregated α-synuclein (Agim and Cannon 2015). Aging is considered the single largest independent risk factor for the emergence of PD (Gasser 2007). The incidence of aging in humans reaches its heights at the age of 70–79 and declines after 80 (Hirsch et al. 2016). Apart from the basic finding that leads to PD, increased oxidative stress and neuroinflammation, iron and neuromelanin accumulation, α-synuclein deposition, and impaired autophagy, it has been studied that physical activity, ibuprofen, smoking, caffeine, and calcium channel blocking agents offer protection against PD, whereas dairy products and pesticides are considered risk factors (Ascherio and Schwarzschild 2016). Underpinning mechanisms that lead to the initiation and progression of PD will pave the way for novel therapeutic strategies toward disease management.

HD and ALS are characterized by autosomal dominant mutation of the Huntingtin gene, and deposition of TAR DNA-binding protein 43-positive protein inclusions and SOD 1 mutations, respectively, are associated with defects in transportation across endosomes, nucleocytoplasmic transport, decreased axonal transport, defects in oligodendrocyte functions, etc. (Bates et al. 2015; Wobst et al. 2017).

## 1.4 Concept of Healthy Aging

Increasing life longevity is not only attributed to biomedical interventions but natural remedies to fight the disabilities associated with aging. Incorporation of a healthy brain completes the exact term "fitness" of an individual. A comprehension of management practices including caloric restrictions (Knorre and Severin 2016),

sirtuins (Grabowska et al. 2017), natural bioactive compounds like curcumin (Yang et al. 2013), resveratrol (Baur and Sinclair 2006), quercetin (Dajas 2012), dietary polyphenols (Kelsey et al. 2010), polyunsaturated fatty acids (Luchtman and Song 2013), and antiaging hormones comprising human growth hormone (Khansari and Gustad 1991), insulin-like growth factor (Miller 2005), melatonin, and estrogen (Froy and Miskin 2007) are all preferred on deck to delay the age-associated disorders and promote healthy aging. Neurodegenerative disorders are chronic with emotional disabilities challenging one's self and societal identity. It is certain that we cannot overcome these disorders completely once caught, but we can delay their onset. We have to cross over the traditional casual treatment practices to socioeconomic grounds as determinants to treat the underlying causatives (Petersen et al. 2015). Application of biomedical imaging has been implemented over the past decades using biomarkers, like amyloid imaging probes used in anti-amyloid therapies for AD, which facilitated the early diagnosis of the disease and hence treating at the starting point (Lerner 2013). However, many careful studies are needed to detect the dose to have that efficacy carries utmost importance. Antihypertensive agents were also identified to reduce neurodegeneration in AD (Yasar et al. 2013), but the current scenario compels us to adapt neural stimulatory activities, including yoga, meditation, physical exercises, caring relationships, and being connected with nature, which can positively boost the brain for healthy living (Boyatzis et al. 2006).

## 1.5 Conclusion

Successful and healthy aging refers to a low risk of diseases, collectively coordinated by physical, mental, and social factors. The conventional thought of aging brings us in a state of age-related stress and depression, increasing our dependency on others, and affects our aging negatively. Science keeps on looking for novel solutions to tackle these disorders by employing earlier detection and subsequent application of prevention strategies. Neurodegeneration is the utmost point of crisis deliberately in need of an integrated approach to find cures, and more scientific and societal practices should be collectively involved and implemented for the much early diagnosis of the diseases.

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