

## Chapter 6

# Neurodegenerative Disorders Progression: From Synaptic Dysfunction to Transmission Failure

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### ABSTRACT

*Neurodegenerative disorders (NDs) are a diverse group of disorders characterized by selective and progressive loss of neural systems that cause dysfunction of the central nervous system (CNS). The examples of NDs include Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Huntington's disease (HD). The aggregated proteins block or disrupt the normal proteosomal turnover, autophagy, and become abnormally modified with time, generating toxicity via pathways thereby resulting in neurodegeneration and neuron death. The chapter highlights the understanding in the areas of AD, PD, HD as illustrative of major research so as to define the key factors and events in the improvement of NDs. It defines the physiological functioning of neural transmission (presynaptic, postsynaptic activity) at neural signaling pathway, then the dynamics of neuronal dysfunctioning and its*

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*molecular mechanism. Further, it also discusses the progression from synaptic dysfunction to transmission failure followed by NDs.*

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## INTRODUCTION

Neurological disorders affect millions of people worldwide which can vary from the nerve disease that causes Tourette's into the serious CNS diseases, impacting either the brain or spinal cord, leading to the neurological or psychiatric deficits. It was observed that up to 1 billion people i.e., almost one in six of the world's population, suffers from either one or the other forms of neurological ailments such as AD, PD, stroke, brain injury, epilepsy, multiple sclerosis, neuroinfections and migraine (*Nearly 1 in 6 of world's population suffer from neurological disorders – UN report, 2007*). Also, it was being estimated in United Nations report issued, that around 6.8 million people worldwide die of these maladies each year. Hence, understanding the neuronal dysfunctioning and resolving its pathological complexity becomes all the way a necessity now. The common aspects of the mentioned disease pathogenesis can be simply summarized with regards to the downstream implications of uncontrollable protein oligomerization and aggregations from post mitotic cells. It was being reported that the polyglutamine protein aggregates in the neurons causes the cells to undergo a stress reaction (Lim & Yue, 2015). Also, a study from the Gladstone Institutes showed for the very first time that mitochondrial damages (brain's cellular power plants) can diminish the energy levels and causes neural dysfunctions in a model of disease (Institutes, 2015). The normal autophagy, proteosomal turnover are disrupted by the aggregated proteins, which modifies with time abnormally thereby, causing toxicity through various mechanisms thereby, leading to neurodegeneration and cellular death (Sweeney et al., 2017). The postulation is coherent with the key genetic similarity between these diseases - e.g., the familial forms are generally caused by autosomal dominant mutation that favours aggregation (in case of PrP, tau, SOD1 and asyn) or formation of disease aggregation prone proteins (in case of CAG and APP repeat sequences) (G. F. Hall, 2011).

The synergistic interaction amongst proteins [synuclein and tau; amyloid precursor protein (APP)/ amyloid  $\beta$  (A $\beta$ ) and prion protein (PrP); tau and PrP;  $\alpha$ -synuclein and PrP] occurs both at interneuronal and cellular level that lead to interneuronal lesion and eventually, pathogenesis of disease (Jellinger, 2012). Amongst all the NDs, AD is the most frequent and clinically known dementia in elderly population. It was recorded that almost 43% of elderly population that are above 85 years are suffering from AD and another CNS associated disorder PD; affects around 1-3% of population over 60 in USA (Qiu, Kivipelto, & von Strauss, 2009). Hence, owing to the above stated facts, the prevention, financial and societal effect of diseases, determination of causes, and exploration of effective treatment has been a foremost emphasis of clinical and basic research globally. Consequently, cellular mitochondria are known to play a key role in age related NDs as they are the important regulators of cell death, a critical characteristic of neurodegeneration (Jellinger, 2010). However, genetic mutations in mitochondrial DNA and oxidative stress cause ageing, attributing massively in initiating the progression of NDs (Lagouge & Larsson, 2013). This chapter focuses and highlights the basic understanding of neuronal irregularities that leads to NDs and its further progression, as illustrative of major research so as to define the key factors and events in the improvement of NDs.

## BACKGROUND

NDs affect the CNS causing the dysfunction of nervous system. These incurable and debilitating conditions are indicated by loss in activity of neurons and are linked with degeneration of affected structures of nervous system (Ghavami et al., 2014). An integral subset of NDs includes dementia associated

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