Chapter

Neurodegeneration: Diagnosis, Prevention, and Therapy

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Abstract

Neurodegenerative disorders (NDDs) are a broad range of pathological conditions which target the neurons, creating problems in movements and mental functions. The NDDs have drawn a lot of attention among the diseases because of its complexity in causes and symptoms, lack of proper effective treatment(s), no report of irreversibility, and poor impact on social and financial aspects. Individual's vulnerability towards the stress-related biochemical alterations including increase in oxidase enzymes' activities and generation of free radicals, abnormal protein dynamics, mitochondrial dysfunctions, and neuroinflammation often lead to degeneration of neuronal cells. Some advanced techniques are now able to detect the development and progression of different NDDs' complications. The current focus of research on NDDs is to establish convenient therapeutic strategies by targeting different aspects including upliftment of cellular defense mechanisms, especially oxidoreductases as a protective tool. This chapter focused on those updated information on the development, diagnosis, prevention, and therapeutic strategies of NDDs.

Keywords: neurodegenerative disorders, proteinopathies, oxidoreductase, neuroimaging, brain mapping, neurotrophic factors, neuroinflammations, epigenetic modulations

1. Introduction

Neurodegeneration refers to a progressive structural and functional loss of neurons causing heterogeneous clinical and pathological expressions followed by deterioration of functional anatomy [1]. This progressive neuronal cell death often leads to various neurodegenerative disorders (NDDs) such as Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), brain trauma (BT), prion disease (PrD), progressive supranuclear palsy (PSP), and spinocerebellar ataxias (SCA), etc., which can be differentiated based on their different pathological mechanistic pathways. It includes associated neuropathology, disease based anatomical vulnerability, and aggregation of some major selective proteins during disease conditions [2]. In the last few decades, several approaches have been taken to understand the mechanisms of neuronal cell death [3]. The oxidative and nitrosative stress due to the overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS) with the deterioration of cellular antioxidant defense systems are found to be the major reasons behind

this neuronal cell damage which might further lead to NDDs [4]. In this context, it is obvious to mention that the oxidoreductase enzymes which are responsible to increase the oxidant level in the cellular microenvironment are one of the major culprits of these sophisticated diseases [4–6]. These pathways and mechanisms of these biochemical processes leading towards the cell deaths are found to be different for various neurodegenerative diseases as observed by their symptoms and exacerbations [4–6]. The common neuropathological hallmarks of such diseases are (a) stress-induced generation of free radicals (b) abnormal protein dynamics, their degradation, and aggregation (c) mitochondrial dysfunctions and (d) neuroinflammation [2] (**Figure 1**). Advanced immunohistochemical and biochemical methods are now able to identify the specific protein abnormalities, related to each of the classes of NDDs [7]. These proteins mostly follow the brain region-specific sequential distribution patterns, suggesting a cell-to-cell propagation [7, 8]. Recently, it is also found that some of the neurodegeneration associated proteins can be detected in peripheral organs and may also present concomitantly in the brain and peripheral tissues [9]. These identified molecular pathological backgrounds of the disease-associated proteins along with the inconsistent clinical symptoms of NDDs create a necessity of proper neuropathological examinations like developments of biomarkers, clinical and neuroimaging studies which finally lead to the accurate diagnosis [9]. The treatment of these neurodegenerative diseases are mostly symptomatic such as dopaminergic treatment for PD and movement disorders, anti-inflammatory and analgesic for neuronal infections and pain, cholinesterase for cognitive disorders, antipsychotic for dementia, etc. though, further progress in therapeutic management is needed to treat many other progressive and serious symptoms of the diseases [10–12]. Integrative treatments along with medicinal therapies are also in the frontline of research to improve the endogenous antioxidant systems targeting the oxidoreductase enzymes and thereby the activity of daily life of the neurodegenerative patients. These integrated treatments act by protecting against oxidative and nitrosative stress related neuropsychiatric disorders, sensory and other symptoms of non-motor fluctuations, fatigue, etc. [11]. In this chapter, the

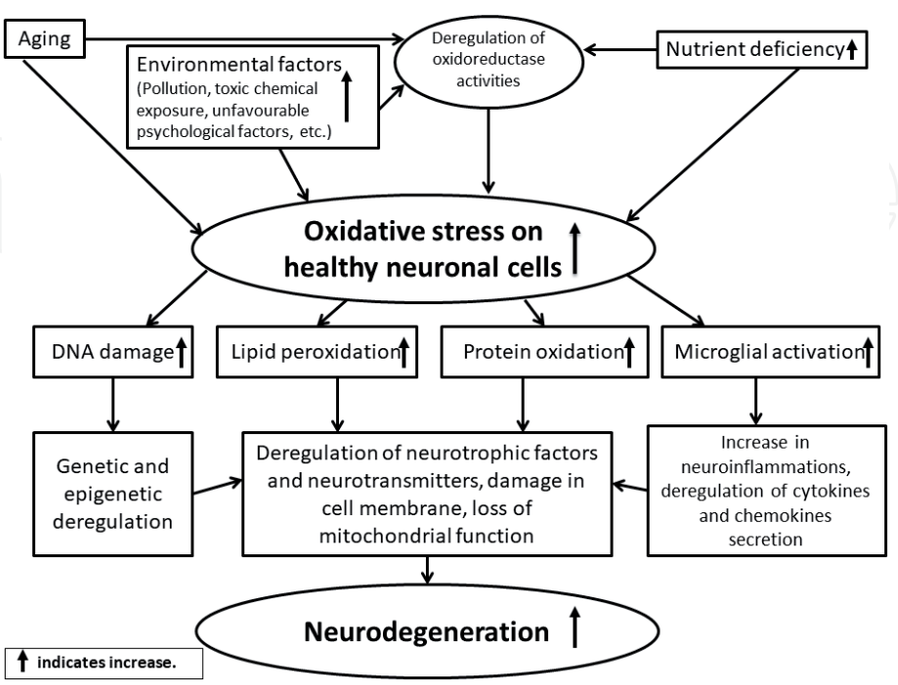

Figure 1.
Schematic presentation of possible steps for the action of different factors involve in the development of neurodegeneration.

diagnostic classification of NDDs, their preventive strategy, and treatment with a special emphasis on the oxidoreductase enzymes are summarized to understand the current progress in the field of NDDs.

2. Role of oxidative stress in neurodegenerations

While aging is the key contributor to most of the NDDs, oxidative stress is the main factor for functional impairment during aging due to the oxidation of lipids, deoxyribonucleic acid (DNA), and proteins in presence of reactive oxygen or nitrogen species (ROS or RNS). Thus, it is not unreasonable to assume that enhancement in level(s) of ROS and/or RNS increase(s) the senescence of cells by secreting pro-inflammatory factors and enzymes followed by cellular degradation [13] (**Figure 1**). S-Nitrosylation reaction plays a crucial role in nitric oxide (NO) bioactivity and is shown to have neuroprotective as well as a neurotoxic role based on the targeted protein [14]. An increase in level of nitrosative stress may affect mitochondrial respiration by inhibiting its complexes I and IV and disrupts the mitochondrial dynamics followed by synaptic injury and neuronal damage [15]. Thus, it may be corroborated that this RNS mediated protein modification is associated with AD pathology, as AD can be characterized by increasing mitochondrial dysfunction [16, 17]. On the other hand, an increase in the level of amyloid-beta (Aβ) and aging aggravate the senescent phenotype and endothelial cell dysfunction and can be characterized by oxidative stress [13]. It is well proved that reduction in oxidative stress can reduce the cognitive impairment and inflammatory processes as oxidative stress enhances the loss of homeostasis [6]. Increased level of oxidative stress also enhances the production of the inflammatory cytokine and finally both affect the cognitive performance in aged individuals [4]. In this context, it is obvious to mention that the involvement of oxidoreductases in oxidative stress is a well-accepted logic-based fact in NDDs [18, 19].

2.1 Role of oxidoreductase in NDDs

Oxidoreductases are the enzymes that catalyze the oxidation–reduction reactions by transferring electrons from oxidant to reductant. It can be classified as oxidases, dehydrogenases, peroxidases, hydroxylases, oxygenases, and reductases. It has been found that increased levels of oxidative stress biomarker glutathione peroxidase (GSH-Px) and reduction in its (GSH-Px) activity are associated with an increase in inflammatory cytokines and both of them has a correlation with the cognitive impairment of elderly individuals [4]. Increased expression of nuclear factor erythroid2-related factor 2 (Nrf2) and reduced level of superoxide dismutase 1 mRNA are associated with cognitive impairments [20]. Nrf2 is the main controller of oxidative response and toxic insults to cells and modulate the expression of the inflammatory, metabolism-related gene [21]. Signaling pathways such as glycogen synthase kinase 3 (GSK-3), nuclear factor kappa light chain enhancer of activated B cells (NF-κB), NOTCH, and adenosine monophosphate kinase (AMP kinase) and Kelch ECH associating protein 1 (Keap1) regulates the Nrf2 activity [6, 22]. It has been observed that Nrf2 deficiency along with amyloidopathy and tauopathy induce neuroinflammation and oxidative stress providing a direct connection between neurodegeneration and oxidoreductase system [23]. Harada et al. [18] have shown a positive association of the NQO2 (dihydronicotonamide riboside (NRH): quinone oxidoreductase 2, or QR2) and PD as the deletion of 29-bp nucleotides in the promoter region of the NQO2 gene associates with the development of PD. In presence of catechol quinones, the over-expression of

NQO2 in brain cells leads to the production of ROS (via the rapid conversion of superoxide radicals into hydrogen peroxide and then into highly reactive hydroxyl radicals)-induced neuronal cell death or neurodegeneration [5]. The other isoform of NAD(P)H:quinone acceptor oxidoreductase (NQO), the NQO1, or NADH quinone oxidoreductase of mitochondria carries the most common Leber's hereditary optic neuropathy (LHON) mutants [24]. The protein disulfide isomerase (PDI) enzyme is another potent oxidoreductase resides in the endoplasmic reticulum, has the ability to catalyze the oxidative folding reactions requires for the maturation of disulfide-bond-containing proteins. It is found to regulate the molecular trafficking along the secretory pathway to prevent the protein misfolding which can mitigate the proteinopathy-induced neurodegenerative diseases (e.g., AD, PD). Monoamine oxidase (MAO) is another oxidoreductase which is predominantly found in the brain regional and platelet mitochondrial outer membrane catalyzes the amine (-NH_2) compound (monoamine neurotransmitters e.g., serotonin (5-HT), dopamine) and formaldehyde and hydrogen peroxide (H_2O_2) as byproducts. During aging the MAO-A activity has been found to be increased in cerebral cortex, hippocampus, hypothalamus, and pons-medulla [25, 26] whereas, decrease in blood platelets [27]. Very limited information are available there about the aldo-keto oxidoreductase (aldehyde dehydrogenase or ALDH, aldose reductase, aldehyde reductase, alcohol dehydrogenase) which can detoxify the reactive aldehyde and ketone bodies in the brain bearing a protective role from the development of aging-induced neurodegenerative diseases, especially AD. The oxidative damage to the polyunsaturated fatty acids (PUFA) generates the 4-hydroxy-trans-2- nonenal (HNE) and its related carbonyl, which creates immunoreactivity. Their elevated levels are found in the brain as well as in cerebrospinal fluid (CSF) of AD, PD, and ALS patients [28]. It (reactive aldehydes) inhibits mitochondrial functions, disrupts cytoskeleton, inhibits glutamate transporters, and also modifies tubulin structure [29, 30]. The aldo-keto oxidoreductases have the ability to detoxify these reactive aldehydes in brain by converting those into corresponding acid or alcohol [31, 32]. The ALDH has been found in the cerebral cortex, hippocampus, basal ganglia, and midbrain, and aldose reductase in the pyramidal cells of cerebral cortex and hippocampal CA1 region, while all of these oxidoreductases are present in cerebellum [19] providing and strengthening the evidence of the fact that cerebellum is less vulnerable in the proteinopathy related NDDs. The xanthine oxidoreductase which converts hypoxanthine to xanthine and thereby to uric acid-producing H_2O_2 as a byproduct can generate superoxide via NADH oxidase activity and similar to ALDH, manganese superoxide dismutase (Mn-SOD) and heme-oxygenase-1 (HO-1) are promptly expressed in reactive astrocytes and found to be present in healthy pyramidal neurons [33, 34].

3. Types of neurodegeneration

NDDs often overlap with each other based on pathology and symptoms especially in multisystem atrophy where several areas get affected at a time making it difficult to analyze clinically [35]. Based on the predominant pathological features and topography of the central nervous system (CNS) during the diseased condition, NDDs have been classified into three major aspects:

3.1 Anatomical classification

The anatomical positions (such as cerebral cortex, basal ganglia, brainstem, cerebellum, spinal cord) in relation to the disease condition (**Table 1**) can be used as

Disease	Main anatomic vulnerability	Symptoms	Main neuropathology	Protein aggregate(s)	Diagnostic approaches	Therapeutic strategies	References
Alzheimer's disease	Basal forebrain, Frontal and Temporal lobes, Limbic structures, Locus coeruleus and Olfactory bulb	Cognitive and functional impairment, Dementia like memory loss, Problems with abstract thinking, Planning, Flexibility, Motor tasks, Neuropsychiatric manifestations and Language problem	Neurofibrillary tangles (NFTs), Neuropil threads, Neuritic and amyloid plaques and Amyloid angiopathy	Aβ 3R+ 4R tau	Anatomical distribution of (a) neuronal tau pathology, (b) extracellular Aβ deposits and (c) CAA	iAβ5 (Chaperon) for inhibiting protein aggregates, Donepezil and Rivastigmine drug therapy, APP regulation by latrepirdine and treatment with cholinesterase inhibitors and HDACi	Finkel, 2004 [36]; Desai and Grossberg; 2005 [10]; Okun et al., 2004 [37]
Parkinson's disease	Substantia nigra pars compacta, Trans-entorhinal region, Motor and Sensory cortex, Prefrontal cortex, Dorsal motor nuclei of the medulla oblongata, Raphe nucleus and Locus coeruleus of the brainstem	Motor symptoms: Tremor (resting), Muscle rigidity, Postural instability, Coordination problem, Slow movements, Bradykinesia and Loss of physical movement, Non motor symptoms: High-level cognitive dysfunction, Psychiatric and emotional changes, Depression, Difficulty in swallowing and speaking, Sensory symptoms and Constipation and/or Urinary problems	Neuronal degeneration of dopaminergic neurons	α-synuclein	Estimation of the activity of terminal dopa decarboxylase (DDC), Evaluation of the availability of presynaptic dopamine transporters (DAT) and Vesicular monoamine transporter 2 (VMAT2) density measurements in dopamine terminals.	Combination of Levodopa and Carbidopa, Inducers of Hsp104 chaperones, Targeting of α- synuclein misfolding with Hsp 70, Treatments with anti-inflammatory drugs against Methyl-4-phenylpyridinium induced autophagy and Knockdown of Sirt2 by siRNA	Brooks, 2005 [38]; Djaldetti et al., 2006 [39]; Quinn, 1995 [40].

Disease	Main anatomic vulnerability	Symptoms	Main neuropathology	Protein aggregate(s)	Diagnostic approaches	Therapeutic strategies	References
Amyotrophic lateral sclerosis	Motor cortex, Brainstem motor neurons and Spinal cord motor neurons	Progressive muscle atrophy, Fasciculation (muscle twitching), Spasticity and Hyporeflexia	Upper and lower motor neuron loss, Bunina bodies, Neuronal inclusions and Astrocytic hyaline inclusions	TDP-43	Morphology and subcellular distribution of protein deposits in neurons and Anatomical distribution of protein deposits	Vitamin E therapy to reduce oxidative stress	Strong, 2003 [41]
Huntington's disease	GABAergic medium spiny neurons (MSNs) in the striatum	Dystonia (involuntary limb movement), Incoordination, Cognitive decline and Behavioral disturbances	GABAergic neurons	Huntingtin	Determining cerebral blood flow (both its decrease and increase) and local brain metabolism, Change in dopamine receptor expression,	Dopamine receptor blockers (e.g. phenothiazines), Targeting of mHTT misfolding with Hsp70, Immunomodulation therapy and Rapamycin-induced autophagy	Andrews and Brooks, 1998 [42].
Prion's Disease	Pyramidal in HP, and Granular neurons in DG	Dementia, Difficulties in walking and speaking, Fatigue, Muscle stiffness, Hallucination and Confusion	Spongiform changes and Prion protein (PrP) accumulation	PrP	Morphology of PrP deposition, Glycosylation pattern and electrophoretic mobility of PK-resistant PrP by using western blot technique, Codon 129 polymorphism and Aetiology if known	RNAi-mediated silencing of host-encoded cellular prion protein (PrPC)	Kovacs and Budka, 2009 [8].

Disease	Main anatomic vulnerability	Symptoms	Main neuropathology	Protein aggregate(s)	Diagnostic approaches	Therapeutic strategies	References
Multiple sclerosis (MS).	Superior medial frontal cortex, Superior dorsolateral frontal cortex, Medial occipital lobe, Lateral occipital cortex, Deep inferior parietal white matter, and Pons	Depression, Fatigue, Anxiety, Personality change, Tremor, Unilateral loss of vision, Pain, Bladder problems, Constipation and Impaired hearing	Inflammation and Demyelination	TDP-43, SOD1, FUS and DPRs	Morphological, subcellular and anatomical distribution of protein deposits	Immunomodulation by beta-interferon, Ocrelizumab etc and Hormonal replacement therapy	Berger and Reindl, 2007 [43]

3R+ 4R tau: 3 or 4C-terminal microtubule binding repeats in Tau protein; APP: amyloid precursor protein; Aβ: amyloid-beta; CAA: Cerebral amyloid angiopathy; DG: Dentate gyrus ; DPRs: dipeptide repeat proteins; FUS: Fused in sarcoma gene; HDACi: histone deacetylase inhibitors; HP: Hypothalamus; Hsp: Heat shock protein; iAβ5: 5-residue β sheet breaker peptide; mHTT: mutant huntingtin; siRNA: Small interfering RNA; Sirt2: sirtuins 2; SOD1: Superoxide dismutase 1; TDP-43: Transactive response (TAR) DNA-binding protein 43; VMAT2: vesicular monoamine transporter 2.

Table 1.
Different types of neurodegenerative diseases and their respective information.

a component to identify the disease and also for its classification [7]. For example, dementia is a pathological condition due to neurodegeneration in the cerebral cortex as observed in AD patients. Similarly abnormal motor functions as observed in PD are associated with degenerations involving basal ganglia including nucleus putamen, globus pallidus, substantia nigra, subthalamic nucleus, red nucleus, and some thalamic and brainstem nuclei, etc. (**Table 1**) [7].

3.2 Based on conformational and biochemical modifications of proteins

Some proteins and their cellular aggregation as identified, are associated with NDDs and found to undergo conformational and biochemical modifications during disease pathology [7]. Proteins such as microtubule-associated protein Tau encoded by MAPT on 17q21 chromosome, Aβ transcript encoded by AβPP gene on chromosome 21q21.3, α- Synuclein encoded by a gene (SNCA) on chromosome 4, prion protein (PrP), encoded by a gene (PRNP) on chromosome 20, Transactive response (TAR) DNA-binding protein 43 (TDP-43) encoded by the TARDBP gene on chromosome 1, etc. are few of the examples. Some hereditary associated proteins encoded by genes that are associated with neurological trinucleotide repeat disorders like ataxins, huntingtin, atrophin-1 are also found as a biomarker of disease identification [44]. Protein deposition pattern in CNS during NDDs are classified into several proteinopathies such as cerebral amyloidoses, tauopathies, α-synucleinopathies, prion diseases, trinucleotide repeat diseases, TDP-43 proteinopathies, FUS/FET proteinopathies, neuroserpinopathy, etc. [7, 44–47]. Only a few numbers of modifications are so far included in the classification and pathological subtyping of the NDDs, e.g. Aβ modification is not included in the classification of AD but the biochemical steps of Aβ aggregation and a different variant of Aβ aggregates have implemented to interpret the early and late phases of AD pathology [48]. Similarly, recent neuropathological studies have revealed that the biochemical classification of tauopathies by analyzing the insoluble and trypsin-resistant tau with varying C-terminal fragments [49]. Tauopathies can be further distinguished by the presence of different ratios of the repeat (R)- and 4R-tau and two or three major phospho-tau bands (60, 64, and 68 kDa) [50]. Other major protein modifications are shown in **Table 2**.

3.3 Cellular pathology

Neurodegenerative diseases can be characterized by the presence of misfolded proteins within or outside of the neurons [51]. Cellular pathology is also an important aspect to distinguish the location of protein deposition at the subcellular level such as nuclear, neuritic (axons or dendrites), cytoplasmic, mitochondria, myelin, lysosomes or in astrocytes, etc. [7]. Charcot–Marie–Tooth neuropathy type 1B (CMT-1B), a hereditary motor and sensory neuropathy, is one such example as it can be identified by the accumulation of misfolded myelin protein zero (mpz) in the endoplasmic reticulum [51]. In superoxide dismutase 1 (SOD1) associated ALS, misfolded SOD1 mutant is found in the cytosol [51]. An aggregate of huntingtin with an expandable polyQ track in the cytosolic and nuclear space of the neuronal cells is a characteristic of HD [52]. α-synuclein, a soluble protein marker of PD is available predominantly in the presynaptic zone of neuronal cells. The complex mechanism of AD consists of binding of Aβ oligomers with several receptors intracellularly. Accumulation of Aβ in the lysosomal compartment followed by a change in its membrane permeability is also identified in AD pathological. Aβ-induced mitochondrial dysfunction by the deregulation of enzymatic activities of the electron transport chain is also identified in AD pathology [52].

Proteinopathies	Proteins	Biochemical characteristics	References
Amyloidoses	Amyloid-beta (Aβ)	• Produced by proteases mediated the sequential cleavage • Most abundant component of Aβ deposit is Aβ 1–40/1–42 peptides along with other available species such as (Aβ 1–37/38/39) • Aβ deposits have resistance against proteinase K	Thal et al., 2015 [48]
	Prion protein (PrP)	• Disease-associated PrPSc is detergent-insoluble and resistance to protease K treatment but not the physiological cellular form of PrP (PrPC) • PrP can be differentiated based on electrophoretic mobility and N-terminal sequence of the core fragments, and the most common PrPres species is PrP27–30. • Other fragments forms are PrP 11, PrP7–8, PrP14, PrP-CTF12/13, PrP16–17, and PrP17.5–18	Kovacs and Budka, 2009 [8]; Duyckaerts et al., 2009 [45]
Tauopathies	Tau	• Most common modification is hyperphosphorylation • Ratio between 3R- and 4R-tau, and two or three major phospho-tau bands (60, 64, and 68 kDa) in Western blot of sarkosyl-insoluble fractions are the major factors for distinguishing tauopathies. • Distinct feature of taupathies are N- and C-terminal truncation, glycation, nitration of tyrosine residues, glycosylation, transglutamination, deamidation; acetylation; oligomer; the banding patterns of C-terminal fragments of tau and the trypsin-resistant band patterns etc.	Lee et al., 2001 [50]; Taniguchi-Watanabe et al., 2015 [49]
Synucleinopathies	α-Synuclein	• Modification occur: phosphorylation at serine 87 and 129 and at tyrosine 125 residue • Various conformation and oligomeric states of synuclein are in dynamic equilibrium state. • Resistance against protease K	Dehay et al., 2015 [46]
TDP-43 Proteinopathies	Transactive response (TAR) DNA-binding protein 43 (TDP-43)	• Modification: phosphorylation on serine 379 (S379), S403, S404, S409, S410 residues • Ubiquitinylation and abnormal cleavage; oligomer; C-terminal fragments detected in disease	Kovacs, 2019 [47]

Aβ 1–40/1–42/1–37/38/39 are different amyloids oligomers consisting different numbers of residue-long proteolytic fragments; PrP27–30,PrP 11, PrP7–8, PrP14, PrP-CTF12/13, PrP16–17, and PrP17.5–18 are different fragments of prion protein consisting of different size (Kda) of fragments; Prp-CFT: C-terminal fragments of PrP; PrPSc: abnormal or scrapie isoform of PrP; 3R- and 4R- Tau: 3 or 4C-terminal microtubule binding repeats in Tau protein.

Table 2.
Biochemical characteristics of some major proteins related to neurodegenerative proteinopathies.

4. Diagnosis of NDDs

The NDDs can be largely differentiated by the anatomical regions showing neuronal dysfunction, biochemical and conformational changes in protein markers and neuronal cell pathologies including the deposition of protein(s), and alteration in genetics and epigenetics [53]. Structural neuroimaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI) are used for diagnosis but due to very low specificity, they have been replaced by new neuroimaging techniques such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) [54]. The functional magnetic resonance imaging (fMRI), another new generation diagnostic approach, identify the correlation of different physiological functions during NDDs rather than direct imagining of neuronal activities [55]. The focus of the new diagnostic researches is to establish easily detectable biomarkers from blood or saliva to distinguish the different forms of neuronal disorders [56]. It has been observed by using fluorodeoxyglucose-PET that the earliest sign of AD is metabolic decline. Detection and identification of small molecule metabolites in the biological samples are called metabolomics, which is another newest cutting edge approach for the diagnosis of neurodegenaration associated metabolic disorders [57]. Genetic markers associated with familiar neurodegenerative diseases are already identified for a different type of disorders such as for diagnosis of AD amyloid precursor protein, presenilin gene mutations and apolipoprotein E (APOE) polymorphism are some of the known genetic markers whereas for PD, α-synuclein protein or PrP gene mutation for the familiar type of prion diseases, etc. have been identified, although their sensitivity and specificity are still questionable [58].

4.1 Application of neuro-imaging in the diagnosis of major diseases due to neurodegenerations

The most frequent CNS diseases are diagnosed by using the following functional neuroimaging techniques:

4.1.1 Parkinson's disease (PD)

PD is known to be progressive as well as a degenerative disorder associated with a loss of dopamine-producing neurons of the substantia nigra and other brain regions [38]. Pathophysiology, progression, and complications of this disease are well understood and identified by neuroimaging techniques. Neuroimaging deals with the detection of the changes in brain structure as well as its region(s) on the basis of changes in brain glucose, oxygen and dopamine metabolism, and receptor binding of dopamine [38]. The functional markers such as (a) the activity of dopa decarboxylase (DDC) terminal, (b) presynaptic dopamine transporters (DAT) availability, and (c) vesicle monoamine transporter density in dopamine terminals (VMAT2) are implemented for neuroimaging (in both PET/SPECT) [38]. DDC works as a catalyst for L-Dopa decarboxylation to Dopamine. Using 6-[18F]-L-dopa PET the activity of DDC can be measured by measuring neuronal loss. 18F-Dopa transfer into 18F-dopamine by amino acid decarboxylase and trapped in synaptic vesicles, whose uptake depends on the presence or loss of nigrostriatal postsynaptic dopamine cell [39, 59]. Similarly, DAT, which helps to clears dopamine after its release in the synaptic cleft, can be used for PD diagnosis. D2–dopamine receptor binding tracers 11C-raclopride-PET and 123I-iodobenzamide (IBZM)-SPECT have been used for the assessment of D2 receptor density and gives good results to evaluate PD patients [38, 39, 59]. VMAT2 is an integral membrane protein

which especially transports dopamine like monoamines into synaptic vesicles. 11C-dihydro-tetrabenazine-PET can be used for its test [38]. In PD loss of 5-HT concentration is observed by 11C-WAY100635-PET and the measurement of 5-HT1A receptor by evaluating the functional integrity of serotonergic neurons [59]. fMRI analysis of PD patients has shown the distinct variation in covariance patterns of the region-based resting-state activity in functional brain regional networks in comparison to the normal brain. The detrimental effect of dopamine replacement on non-motor brain functions due to the alteration of the physiological pattern of dopamine signaling can also be proved by fMRI studies [60]. This suggests functional changes between the three different brain-related disorders. PD can be characterized by the activation of the neuroimmune system in microglia followed by a loss of neurons in substantia nigra [61]. 11C-PK11195 is known to enable the detection of increased signals in substantia nigra which reflect local degeneration as a consequence of PD [38]. In addition, the significant reduction in metabolomes like catecholamines [homovanillic acid (HVA), dihydroxyphenylacetic acid (DOPAC), L-dopa, etc.) has also been observed during PD [62]. NMR metabolomics based study has helped to differentiate PD from non-PD patients by detecting the presence of metabolomes (like creatinine, glucose, lactate, 3-hydroxyisobutyric acid and 3-hydroxyisovaleric acid etc.) in CSF [62]. The presence of kynurenine in the blood of PD is proved to be potential biomarker candidates [62].

4.1.2 Alzheimer's disease (AD)

Structural neuroimaging with CT and volumetric MRI has an application on AD related cerebral atrophy and measurement of cerebral blood flow or regional glucose and oxygen metabolism [63]. MRI helps to measure the memory forming zone of CNS i.e. hippocampus and cortex-structures in the temporal lobe and further helps to differentiate between AD and other dementia [64, 65]. By using magnetic resonance spectroscopy (MRS) the information about concentrations of tissue substrate or metabolite during AD and MCI (mild cognitive impairment) can be identified by using N-acetyl aspartate as a marker [64, 66]. Quantification of amyloid deposition by tracing the amounts of radioligands *in vivo* is also possible by PET and SPECT. PET usually detect the metabolic uptake of fluorine 18 [18F]-labeled 2 fluorodeoxyglucose (2-deoxy-2-[18F]- fluoro-D-glucose- FDG) and blood flow in patients with dementia [64, 67]. The fMRI techniques in AD diagnosis is implemented in cerebral blood flow (CBF) and cerebral vasomotor regulation (CVR) mapping. This limitation in CVR has been observed in the APOEε4 gene carrying early-onset AD patients with vascular dysfunction, which occur due to the astrocytic end-feet swelling, degeneration of pericyte, hypertrophy of basement-membrane as well as due to the abnormalities in the endothelial-cell metabolic. Non-invasive fMRI is a major tool for the diagnosis of AD by identifying such changes in CVR mapping [55]. In the AD brain, the most characteristic feature and useful biomarker are amyloid plaques consisting of Aβ protein, dystrophic neuritis, inflammatory factors, and cellular material inside and outside of the neurons [68]. Tau tangles are also associated with AD and composed of paired helical filaments (PHF) derived from abnormally hyperphosphorylated microtubule-associated protein tau [69]. Radiotracers such as [18F]-BAY94–9172, an Aβ ligand, have been used with PET to differentiate between AD and frontotemporal dementia patients [66, 70]. PET studies with the application of [11C] PIB, a derivative of thioflavin-T amyloid dye that binds to Aβ plaques but not tangles, show more retention in the cortical zone of frontotemporal dementic brain when compared to AD brain [64, 65]. 18F-DDNP – PET scanning helps to compare AD, MCI, and controls having intact cognitive functions [71, 72]. The plasma metabolomics biomarkers including

glycerophosphatidylcholines, asparagine, acylcarnitines, and asymmetric dimethylarginine (ADMA) are identified as a predictive marker of plasma which can predict the risk of conversion from cognitively normal individuals to AD [57]. Reduction in N-acetyl aspartate in the brain can be correlated with neuronal and mitochondrial dysfunction during AD. Acylcarnitine, sphingomyelins, glycerophospholipids found to be increased significantly in the CSF of AD patients in comparison to normal patients [57].

4.1.3 Huntington's disease (HD)

HD is a dominantly inherited, autosomal, NDD characterized by motor, cognitive, and emotional abnormalities [42]. In the early course of HD, no structural changes of the brain can be observed by CT and MRI while only in later stage atrophy has been observed in the caudate and frontal cortex [73]. PET study can provide information by diagnosing HD as early as 9 to 11 years before the first symptoms appear [74]. PET with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (^{18}F-FDG-PET) is also used to detect the reduced striatal glucose metabolism in early HD which further causes bradykinesia, dementia, and putamen hypometabolism connects with chorea and eye-movement abnormalities [42, 75]. HD has also been found to be associated with structural loss of dopamine (D1, D2) receptor-expressing medium spiny neurons from the striatum. The damage can be estimated by using radiolabelled dopamine antagonists [11C] raclopride and by observing the binding potential (BP) of dopamine receptors which help to assess the neuronal damage [42]. Further, PET study using [11C] diprenorphine as a tracer has shown a mild loss of opioid receptors in the striatum in HD patients [42]. The accumulation of active microglia due to neuronal loss can be seen with the help of 11C-(R)-PK11195 as a tracer in the striatum, globus pallidus, and frontal cortex in HD patients [76]. fMRI has applied to diagnosed HD by various cognitive paradigm including maze learning, serial reaction time, working memory etc. fMRI blood-oxygen-level-dependent (BOLD) signal response is also applied for correlation between different regions in HD patients [74]. HD is associated with metabolic and energy pathways alterations. After studying various metabolomics Mastrokolias et al. [77] have found that the deregulation of phosphatidylcholine metabolism is a prominent plasma biomarker of HD.

4.1.4 Amyotrophic lateral sclerosis (ALS)

ALS is a motor neuron disease (MND) associated with progressive deterioration of the corticospinal tract, brainstem, and anterior horn cells of the spinal cord [78]. Cortical atrophy is observed in late ALS which can be assessed by structural MRI of ALS patients' CT studies. The increased population of microglia during ALS can be observed by radiolabelled PET ligand [11C] (R)- PK11195 which selectively binds with the peripheral benzodiazepine binding site (PBBS) of microglia [79]. ALS can be also diagnosed by the measurement of postsynaptic dopamine D2 receptor binding abilities. 123I-benzamide (123I-IBZM), a specific binding substance with D2 receptors shows less receptor binding during ALS when investigated using SPECT [80, 81]. PET studies show a decrease in 11C-flumazenil (a radiolabelled antagonist of benzodiazepine receptor) binding in the primary sensory, premotor, prefrontal, thalamic, and parietal regions during ALS [78, 82]. Both 123I-N-isopropyl-p-iodoamphetamine (123I-IMP) and 99mTc-hexamethyl propylene amine oxime ([99mTc] –D, L- HMPAO) are markers which have been used to determine reduced fronto-temporal blood flow as well as glucose metabolism by SPECT studies [41].

4.1.5 Multiple sclerosis (MS)

MS is characterized by demyelination of neurons in the CNS, with the formation of plaques or lesions [43]. MRI studies show these lesions are dynamic in different stages of the disease. Neuronal loss and brain atrophy are not visible in the early stage of MS by MRI scans [83]. Decreased regional and global CBF and cerebral metabolic rate of glucose (CMRglc) can be observed by PET imaging using 18FDG as a detection agent. Although the differentiation between acute and chronic MS is tough for the SPECT study with the help of Tc-99 m-MIBI as a radiopharmaceutical, which in fact shows multiple accumulation points in acute MS but not in chronic MS [84]. Binding potential of microglial peripheral benzodiazepine binding sites (PBBS) towards [11C] (R)-PK11195 can be applied as a determinant factor of MS, like other neurodegenerative diseases [83, 85]. Application of fMRI in MS has been recently applied to assess MS-associated modification of cervical cord in the patient. This study also helps to identify the brain regions involved in the tactile and proprioceptive stimulation during AD pathology [86]. Mangalam et al. [87] have performed a study to find out the MS-based untargeted metabolic alterations in bile acid biosynthesis as well as the metabolism of histidine, taurine, tryptophan linoleic acid, and d-arginine.

4.2 Anatomical identifications of neuronal losses in relation to clinical symptoms

Identification of anatomical positions is needed for understanding the early symptoms. For example, brain regions such as the entorhinal cortex, neocortex, hippocampus, limbic system are responsible for symptoms like cognitive decline, dementia, and other high-order brain functions alterations whereas basal ganglia, thalamus, brain stem, and motor cortical areas are mostly responsible for disturbance in body movements. Combinations of these types of symptoms are mostly observed during the progression of diseases following region-specific neurodegenerations [7]. One of the conventional approaches to understand neuroanatomy is brain mapping which helps to localize the disease-related changes [88, 89]. Characterization of brain regional anatomical changes in diseased conditions is a fascinating and advanced approach of current neuroscience research [90]. Earlier the identification of neurofibrillary tangles in the cortex and the hippocampus due to Alzheimer's were studied by region-of-interest technique (ROI). These techniques (ROI) can be implemented to compute the overall volume for a particular brain structure, based on the manual or automatic positioning of the sections' MRI serially for a subject by using already existing anatomical protocols [91]. Though the prior knowledge of anatomical structures makes ROI-based analysis a strong and useful approach, the lack of detailing in the investigation of the underlying complex structure makes this method less advantageous for diagnosis [92]. Like in AD patient ROI technique is capable of establishing the hippocampus and entorhinal cortex as most prominent imaging biomarkers but this technique is not useful to investigate the underlying complex structure of the hippocampus for further diagnosis [91–93]. Another newer image analysis technique is Voxel-based morphometry (VBM) able to identify cortical and subcortical degeneration simultaneously, providing significant insight changes in gray matter in AD and MCI [94]. VBM can be implemented to classify MRI maps into individual maps of gray matter, white matter, and CSF tissue classes followed by creating an alignment of gray matter maps and then smoothened it with the help of filters. The corresponding cognitive score has been statistically assessed using multiple regression analysis. The general linear model used to fit with gray matter density at each image location or voxel related to diagnosis, cognitive scores, etc. [95, 96]. Several brain regional gray matter atrophy such as

temporal, posterior cingulated, precorneal cortex in AD and normal aged persons has been documented by using VBM studies [97]. The application of VBM has also been observed to investigate the effect of aging and gender on spatial profiling in normal subjects [96] as well as in the frontotemporal zone of PD, and Lewy body dementia, and also in herpes simplex encephalitis [98–100].

The limitation of VBM is inherently low spatial resolution due to spatial smoothening to achieve inter-individual cortical variability [101]. VBM study is also not optimal for analysis of gray matter atrophy as highly convoluted features that appeared for the Gyral and sulcal region cannot be readily distinguished leading to a lack of detecting and localizing the subtle cortical differences [89].

4.3 Brain mapping: a diagnostic tool for neurodegenerative diseases

Brain mapping techniques rely on a mathematical computation of anatomy where brain surface and its volumes are represented as 3D complex geometrical patterns mesh models, averaged, combined across subjects and can be statistically defined [89]. The technique implies transformable and deformable templates which can be transformed into brain shape for studies by constraining surface landmarks (e.g., sulci) or alignment of surface-specific geometrical patterns (e.g., gyri) and helps to co-localized cortical and subcortical regions along with cortical thickness, gray matter density, functional activations, etc. by improving the identification of cortical and subcortical changes associated to the diseases [102]. Localization of changes by cross-sectional and longitudinal imaging is done by tensor-based morphometry (TBM), a newer approach to map the changes in the brain over time. This method has been found to be sensitive, with high throughput, and attractive for gauging brain changes in larger study populations. In cross-sectional studies, where many individual images are matched to a common brain template to compare the systematic volume and shape between control and diseased individuals, TMB has been found to be effective and helps to clinically correlate the different disease conditions like Fragile X syndrome 56 and Williams syndrome, etc. [103]. TBM can detect and visualize subcortical nuclear as well as structural gray and white matter by using newer statistical methods [103].

4.3.1 Application of brain mapping in AD

Radial atrophy mapping of the hippocampus has been first applied by Thompson et al. [104] for the diagnosis of AD and has shown distinct differences between normal elderly and AD patients. Later on, Frisoni et al. [105] have demonstrated that the CA1 area and parts of the subiculum using the same technique and showed AD cases have 15–20% atrophy in relation to the normal controls. Apostolova et al. [88] have shown that patients with MCI have more severe involvement of CA1 and subiculum atrophy which are likely to convert into AD at a later age. Apolipoprotein E4 (APOE ε4) a prominent genetic risk factor for sporadic AD carriers, has a higher hippocampal atrophy rate than non-carriers as observed by longitudinal MRI study. Further, Bookheimer et al. [106] by cortical thickness study have shown that cognitively normal APOE ε4 carriers have a significantly thinner entorhinal cortex and focal hippocampal atrophy in comparison to normal non-carriers. Thompson et al. [104] have also reported based on the comparison of baseline grey matter density map a significant atrophy in lateral, temporal, parietal, and parieto-occipital cortices in AD patients. Brain mapping by computational anatomy techniques has significantly improved sensitivity for the detection of differences in the disease-induced groups. The study between amnestic MCI and mild AD subjects has shown a highly significant greater cortical atrophy in AD patient

despite a small cognitive difference between these two groups [88]. It has also been observed that in sporadic early-onset of AD (EOAD; <65 years of age) and late-onset of AD (LOAD; >65 years of age), subjects can also be differentiated by severity and localization of cortical atrophy. While EOAD shows widespread atrophic changes, LOAD subjects show lower rate and more focal pattern of entorhinal, para-hippocampal, inferior temporal, posterior cingulate/precuneal, and lateral temporal changes, suggesting younger AD subjects have displayed higher cognitive reserve and tolerance to pathological burden as cortical neurodegeneration correlates with cognitive declines [105].

4.3.2 Application of brain mapping in dementia

Dementia with Lewy bodies (DLB) is associated with some of the features such as cognitive decline, early-onset hallucinations and delusions, Parkinsonism, and a fluctuating course. Pathologically hallmarks for DLB are synuclein-rich intracellular deposits known as Lewy bodies is often observed as a hallmark of DLB in patients as well as in few cases of AD. It has been observed that a distinct cortical atrophy pattern i.e. hippocampal and inferior temporal preservation along with midbrain atrophy occurs in DLB but not in AD when studied by VBM [100]. Ballmeier et al. [107] have mentioned that the preservation of the temporal and orbitofrontal cortices in demented subjects is also a distinct feature of DLB.

5. Preventive measures for neurodegenerative diseases

The estimated number of total dementia cases globally is around 50 million among which 60% of the cases are from low or middle-income countries and also 10 million new cases are reported globally every year as per the recent report of WHO. Hence, the demands of health care and social services are huge and need constant surveillance to decrease the rate of incidence of this type of life-threatening diseases as well as its associated expenses. It has been observed that up to 10 years before the diagnosis of dementia, cognitive impairment is likely to appear in individuals and it declines sharply in the final stage of 3 years [108]. Individuals with deficits in vitamin B12, folate, and thyroid-stimulating hormones (TSH) are found to involve with poorer cognitive performances [109]. Elevated levels of serum-homocysteine and cardiovascular diseases are also responsible for cognitive impairments [110]. Depressed mood, hip fracture, polypharmacy, history of psychoses are the reasons behind cognitive impairment without dementia (CIND) in older age and the low education, depression, APOE ε4 allele, medicated hypertension, midlife elevated serum cholesterol, and high diastolic pressure, as well as diabetes and anticholinergic medication, are responsible factors for mild cognitive impairment (MCI) [111, 112]. The strongest risk factor of dementia and AD is age and lifetime cumulative multiple risk factors like genetic susceptibility, environmental exposure, and biological factors etc. are also needed to be considered for identification of preventive measures [113, 114]. For example, genetic and environmental factors are responsible for Familial AD as reported by many and found to be happening in 58% of AD cases [114, 115]. The involvement of APOE ε4 allele as a genetic factor as well as some other genes in AD is well established and, APOE polymorphism can partially explain the familial aggregation of AD in 15–20% of AD cases which generally affect 75 years or older patients [116, 117]. Vascular risk factors and AD or dementia are also found to be associated and the control of amendable vascular disease-associated risk factors has found to offer preventive measures for AD [118]. Such as controlling high blood pressure,

diabetics, and mid-life obesity are important interventions and found to show a better score in cognitive tests and reduce the risk of dementia and AD in very old individuals [118]. One more important aspect is psychosocial factors and it has been reported that attending higher education in early-life, work complexity in adult life, intellectually stimulating activities are also found to help in delaying the onset of dementia [119]. Physical activities have a beneficial effect on mental health [120]. It has been reported by Alzheimer's associations [120] that mentally, physically and socially active lives have the potential to postpone the onset of clinical dementia by 5 years and substantially decrease the number of dementia cases in the community.

5.1 Role of diets and micronutrients in the prevention of neurodegenerative diseases

Dietary components are found to be effective in the prevention of neurodegenerative diseases [121]. It has been observed that docosahexaenoic acid (DHA), an n-3 polyunsaturated fatty acid, enriched diet such as fish (fatty or blue species), shellfish, and algae [122] plays a relevant role in the preservation of histopathology of the neuronal tissue and helps in memory and learning maintenance [123]. Apart from that, polyphenols, curcumin like food components have neuroprotective properties [124, 125]. Polyphenols are a natural antioxidant and show activities on chelation, scavenging free radicals, survival gene activations, cell signaling pathways, and also regulating mitochondrial function by the ubiquitin-proteasome system [124]. On the other hand, curcumin is an anti-amyloid drug and responsible for reducing oxidation of protein and also reduce pro-inflammatory cytokines interleukin-1beta in AD-induced transgenic mice brains [125]. Deficiency of vitamin B, C, and E are associated with AD development [126]. Some mixed results in this regard have been observed in several clinical studies [127, 128]. As reported, a lower level of dietary and supplemented folic acid is associated with AD pathology and lack of folic acid due to malabsorption and malnutrition can increase the chance of AD by two folds in the elderly [127, 129]. Some studies have found no significant role of Vitamin B9, B12, C, E in AD pathology, whereas the other study gives evidence that Vitamin C and E have a neuroprotective effect on AD [128]. It has also been studied that while sufficient intake of vitamin E, omega-3 fatty acid and omega-6 fatty acid, vitamins A, C, and whole grains increase neuronal activation, food component like saturated fatty acids, cholesterol and sodium significantly lower the neuronal activation and gray matter volume [130]. One more significant effect of diet on neuronal health is observed when a calorie-restricted diet is consumed by aged individuals [131]. It has observed that calorie restriction augments brain-derived neurotrophic factor (BDNF), induces sirtuins a silent information regulator proteins responsible for the regulation of life span, repair, and protection of DNA, etc. [132]. While some dietary components' actually have the preventive function on neurodegeneration on the other hand some obesity-induced dietary components act oppositely and increase the risk of AD, PD, and neuroinflammatory disease [133].

5.2 Physical exercise for prevention of neurodegenerative diseases

Physical exercise for short term or long term has been found to be beneficial on neurodegenerations and cerebrovascular diseases as observed in both animal and human model [134]. Physical exercise and the expression of different neurotrophic factors [like BDNF, insulin like growth factor-1 (IGF-1), vascular endothelial

growth factor (VEGF)] are found to be associated, and hence promote neural plasticity and neurogenesis in the hippocampus [135]. It has also been observed that upregulation of BDNF in circulation as well as in the brain can be induced by exercise which can be corroborated with an increase in cognitive function [135]. Due to exercise metabolite-like ketone bodies accumulates in the hippocampal region of the brain which alters BDNF promoter and promotes BDNF expression [136]. BDNF expression is regulated by various genetic factors and pathways like Val66Met mutation [137], PGC-1α/FNDC5 pathway [138], APOEε4 allele carriers [139] and methyl CpG binding protein 2, etc. [140]. Reports are also available on the effect of exercise-induced increase level of VEGF in relation to the reduction in ischemic injury and improvement in cognitive performance. This may be due to an increase in progenitor cell proliferation and all the cell differentiation in ischemic penumbra [141]. Some data has depicted that exercise-induced muscular VEGF increases the level of VEGF in the hippocampus. However, this VEGF helps in neurogenesis and angiogenesis in the ischemic brain followed by improved cognitive activity [142]. The muscle-derived IGF-1 has been found to increase IGF-1 permeability via BBB by increasing the IGF-1 receptor expression in BBB followed by IGF-1 concentration in the hippocampus possibly by regulating IGF binding proteins (IGF-BPs) [143]. Alteration of cytokine production by exercise can also restore the IGF-1 level followed by a reduction in neurodegeneration [143]. Physical exercise, as reported, when used as an adjuvant therapy of psychotropic drugs gives better anti-depressant and anti-anxiety outcome and also effectively reduces dementia [144]. Production of several myokines in muscles (like PGC-1α, Irisin and Cathepsin B, etc.) is promoted by exercise. Myokines that are beneficial for the brain (fibroblast growth factor 21 (FGF-21) and SPARC etc.) also generate after exercise. Serotonin (5-HT) concentration generally increases after exercise in serum, whole blood, and also in urine [145]. This peripheral 5HT level is found to be correlated with an increased level of 5-HT in the brain [146]. Exercise is also associated with a decrease in AD specific deposition of Aβ and tau pathology in the brain [147]. High-intensity exercise provides an improvement in PD associated impaired motor functions [148]. Exercise can also reduce the loss of dopaminergic neurons and fibers and decrease α-synuclein in the nigrostriatal region as observed in animals [149].

6. Therapeutic strategies

Conventional therapies such as cholinesterase inhibitors for AD or Levo-dopa for PD provide symptomatic relief but not on effective disease progression. Advancement in the knowledge of the neuro-molecular mechanism of NDDs has helped to develop new drugs to counteract pathological aggregation of the protein [150]. The prevention of abnormal protein aggregation or targeting of misfolded proteins for their degradation by new therapeutic agents is a potential field of recent researches [151]. Reports are also available on the inhibition of fibril formation by several compounds like antibodies, molecular chaperones, nanoparticles of polyphenols, metal chelators, and tetracyclines nanoparticles by inhibiting the aggregating pathways of different amyloidogenic proteins, such as Aβ, α-synuclein, PrP protein, etc. [152]. But the most challenging part of therapeutic strategies are (a) prevention of the formation of oligomers or converting aggregation process into alternative non-toxic pathways (b) transporting the therapeutic agents through the blood–brain-barrier (BBB) and (c) delivery of nanoparticulate drugs to the targeted neuron to reduce dose-dependent toxicities and side effects.

6.1 Available treatment paradigm

Among the few food and drug administration (FDA) approved drug regimen Donepezil and Rivastigmine like acetylcholine esterase inhibitors are used as palliative treatment which help to reduce the progression of AD but not for the long-term [36, 153]. A combination of levodopa and carbidopa has been successfully delivered via the BBB to treat PD patients. The drugs act by converting into dopamine after decarboxylation in the substantia nigra of the PD patient and increase the level of dopamine in that zone for the first few years of treatment after consecutive consumption [40]. Dopamine agonists such as Pergolide, Bromocriptine Parlodel also have therapeutic efficacy but show cardiovascular and endocrinological problems [154]. In HD, reserpine, or dopamine receptor blockers (i.e. phenothiazines) are used to impair dopamine transport and to reduce overactivity in dopaminergic nigrostriatal pathways [155]. In MS, the preventive measures taken to combat the relapse are prednisone to reduce inflammation, beta-interferon, Ocrelizumab, glatiramer acetate, alemtuzumab, mitoxantrone for immunomodulation, and Ocrelizumab for reducing the primary progression [156].

6.2 Future strategies

Effective treatment of NDDs needs identification and mitigation of risks, complete cure, or at least a long term relief from the symptoms that need to be achieved despite all the advancement of genetic, biomolecular, and pharmaceutical sciences. Some of the strategies are designed or may execute in lower animals but clinical trials and human applications are yet to be achieved. Some novel therapeutic strategies are summarized below.

6.2.1 Inhibition of disease-associated protein deposition

Protein misfolding are occurred due to gene mutations, oxidative stress, aging, altered cellular temperature, pH, etc. [157]. The misfolded proteins are often partially unfolded by molecular chaperones and then go through a self-rearrangement to form oligomeric aggregates that are finally converted into amyloid fibrils [158]. Accumulations of such protein aggregates are often found to be in relation to amyloidosis of the CNS as well as symptoms of neurodegeneration [159]. Synthetic chaperons or short peptides with a recognition motif of misfolded proteins have therapeutic potential to disaggregate this protein aggregation during amyloidosis. Heat shock protein 104 (Hsp104) one of the major molecular chaperones, has been found to be efficacious to disaggregate proteins aggregates in yeast cells [160]. Hsp104 has shown to eliminate various amyloid conformations and reduce deposits of pre-amyloid oligomers by binding with the protein fibril and blocking the aggregation process [160]. One variant of Hsp104 has properties to dissolve α- synuclein aggregates in the PD model. Hsp70 and its related compound also have neuroprotective roles as found by in-vitro and in-vivo studies (**Figure 2**) [160]. Hsp70 is also responsible for restoring Tau homeostatic [161]. In-vitro and in-vivo studies have revealed that Hsp70 and related compounds help to clear Aβ depositions and restore Tau homeostasis [160, 161]. The proposed therapeutic strategies are tabulated in **Figure 2**. HD is associated with polyQ induced misfolding of mHTT mutant Huntington which can be the target and inhibit by Hsp70 [162]. Curcumin or epigallocatechin gallate have Hsp70 simulating properties resulting in a reduced level of neuronal death followed by improved cognitive and motor deficits [163]. On the other hand, α-synuclein misfolded protein aggregation is associated with PD, and

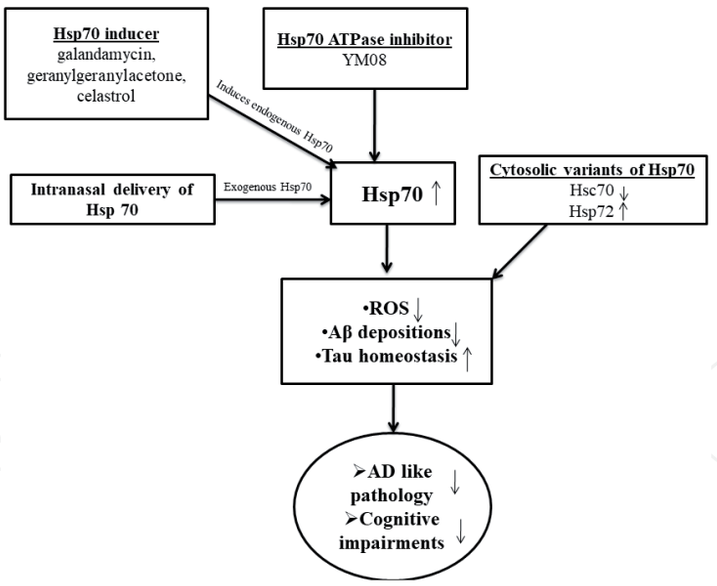

Figure 2.
Different strategies for inducing Hsp 70 as molecular chaperone in AD brain.
Molecular chaperones of heat shock protein 70 have neuroprotective properties such as, maintenance of the tau homeostasis, and decrease in the reactive oxygen species (ROS) generation and amyloid-beta (Aβ) depositions which are related to both AD pathology and cognitive impairments. There are other cytosolic isoforms of Hsp 70 i.e. Hsc 70 and Hsp 72 whose downregulation and upregulation respectively also show similar effect on the above mentioned parameters. Neuroprotective effect of Hsp 70 can be achieved by (a) targeting Hsp 70 ATPase using its inhibitor, YM08, (b) Hsp 70 inducers (for example, galandamycin, geranylgeranylacetone, and celastrol) or (c) intranasal delivery of Hsp 70. ↓ and ↑ indicate increase and decrease respectively.

Hsp70 can bind with α-synuclein and halt the further misfolding of α- synuclein followed by refolding [164]. In this context, it may be mentioned that specific Hsp and related chaperones significantly contribute to targeting protein aggregates (mHTT, α-synuclein, etc.) specific to NDDs, and the development of these Hsp stimulant can be beneficial for future therapies [165].

6.2.2 Neuroimmunomodulatory therapies

Neuronal death and neurodegeneration are in connection with the vicious cycle of inflammation especially when inflammatory mediators stay in the tissue for a longer period. AD, PD, and HD cases express higher plasma and CSF concentrations of proinflammatory cytokines, such as IL-6, TNF-α, IL-1β, IL-2, IL-6, and cyclooxygenase-1/2, etc. [166] whereas, anti-inflammatory cytokines and growth factors (IL-10, TGF-β, CD206, etc.) producing microglia becomes lower in number in such patients [167]. The monocytes isolated from the carriers of the HD gene, express the mutant Huntingtin protein and show hyperactivity to lipopolysaccharide stimulations [168]. Thus, it may be concluded that the hyperactive immune system is an important feature of HD pathogenesis and its associated immunomodulators can be used for potential HD treatment. The presence of CD8+ and CD4+ peripheral lymphocytes in substantia nigra has been found in post mortem brains of PD patients [169]. Anti-inflammatory drugs such as minocycline, resveratrol, tanshinone, and silymarin have therapeutic promises against PD by blocking the activation of NADPH oxidase and microglial activation and pro-inflammatory cytokine release [12, 157]. Apart from that, it has also been investigated that the monoclonal antibodies against the α-synuclein not only reduced protein propagation and amyloid formation [170] but also ameliorated dopaminergic neuronal cell loss and improved PD-like pathologies, followed by improving motor deficits in PD induced mouse [170].

6.2.3 Autophagy

Neuronal cells are subjected to autophagy but they have a very strong lysosomal system which is effective for the removal of protein aggregates and dysfunctional mitochondria as well as the rapid removal of the autophagosomes [171]. The autophagy regulating gene mutation often leads to NDDs like AD, ALS, and PD as a consequence of large gathering of the debris of dysfunctional organelles and undiluted waste proteins [172]. The factors responsible for the suppression of autophagy followed by suppressing neuronal functions and plasticity are stress signals, hypoxia, mechanical damages, decreased level of amino acids, etc. [173]. Mutation of autophagy-related genes has shown neurodegeneration in lower animals like mice and flies [174, 175]. A promising therapeutic strategy is a drug-induced autophagy in neurogenerative patients for the removal of abnormal proteins as observed in animal models. One of the recent examples of such drug-induced autophagy is methyl-4-phenylpyridinium (MPP+) which induces apoptosis in dopaminergic neurons by disrupting the complex I of the electron transport chain of mitochondria of mouse Parkinson's Models [176]. Similarly, the antihistaminic drug, Latrepirdine shows a regulation of APP in the AD mice model [177]. Drugs like calcium channel blockers and USFDA approved rapamycin show potential to stimulate the autophagic process followed by the clearance of mutant huntingtin protein in lower animals [178]. Rapamycin is also able to reduce Aβ-induced cognitive deficits of AD by activation of the AMPK-mTOR signaling pathway in aged as well as Type 2 Diabetes Mellitus-induced AD cases [179]. mTOR signaling has the ability to form autophagic vacuoles, mitigating tau and Aβ deposition and controlling the apoptotic pathways. Metformin has been found to involve in autophagy by AMPK-dependent mechanism of HD as well as dephosphorylates neurofibrillary tangles of tau in AD and is established as a potential therapeutic agent for NDDs [177].

6.2.4 Neurotrophic factors and possible strategies for neurogenesis

Dysregulation of the neurotrophic factors which are the molecular aids of neuronal functions such as differentiation, growth, etc., is associated with NDDs [180]. The affected region of the brain starts losing neurons and glia in absence of functional regulation of these molecules [181]. Some Factors such as nerve growth factors (NGF), BDNF have the ability to bind with tyrosine receptor kinases, inhibit apoptotic signals, and promotes cell survival by promoting tissue growth by cell proliferation [182] and also their absence play a prominent role in neurodegenerative diseases [183]. A decreased level of NGF in AD patients induces cellular death followed by loss of neuronal functions whereas a decrease of BDNF in substantia nigra does the similar in PD patients due to degeneration of synaptic connections [184]. An increase in the level of these neurotrophic factors in the degenerated brain regions could be a possible therapeutic strategy although their larger size and polar nature make them unsuitable for transport through BBB and difficult to target [185] although gene delivery injection and neurotrophin mimetics are already under investigations [183]. Another important marker of NDDs is the deficiency of neurosteroids during AD [37], PD [37], HD [186], and MS [187] which can be defended by hormonal replacement therapy and found to be beneficial in AD, PD, HD, and MS patients [188].

6.2.5 Insulin associated neurodegeneration

Insulin signaling in CNS is responsible for differentiation, proliferation, neurite growth, and shows neuroprotective as well as anti-apoptotic activity [189]. The

structural and functional integrity of synapses, neurons, and neuronal circuits followed by memory and learning are depend partially on Insulin and affected by diabetes mellitus and metabolic syndromes [189]. Insulin resistance in the brain is also associated with an increased level of phospho-Tau and Aβ42 [189]. Evidence is there of decrease in levels of insulin in the brain and CSF during AD with an increase in Aβ42 and advanced glycation [189]. Insulin administration enhances Aβ42 clearance and improves working memory and cognition [189]. Insulin receptor-associated genes IRS-1 pSer616 and IRS-1 pSer636/639 have been identified in relation to Aβ oligomer levels and function as a biomarker for AD [190]. Antidiabetic drug Metformin is reported to inhibit cognitive decline which may have some connection with the insulin signaling pathway in CNS although needs further investigation [191].

6.2.6 Cholinergic system in AD

The connection between the cholinergic system and AD has been hypothesized as presynaptic cholinergic markers are found to be depleted in the cerebral cortex during AD pathology [192], nucleus basalis of Meynert (nbM) in the basal forebrain undergoes severe degeneration in AD [193], and memory gets weaken by the cholinergic antagonist while agonists have the opposite effect [194]. Cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine have been found to improve significantly the cognitive activity related to AD [195].

6.2.7 Targeting oxidoreductases

A very limited information are available about targeting oxidoreductases to inhibit the proteinopathies and consequent neurodegeneration. Among the free radical generator, the NOX bears a significant role in oxidative stress-induced neurodegeneration. The pharmacological NOX inhibitors have been found to improve different NDDs and it is well-reviewed by Barua et al. [196]. The PDI, as discussed before is associated with different proteinopathies (like AD and PD) and its attenuation could be a promising approach to counteract the proteinopathy-induced neurodegeneration. Polyphenols curcumin, from a turmeric (*Curcuma longa*) spice and masoprocol (from *Larrea tridentata*), have found to restore the ROS-induced chaperone damage, protein misfolding, and thereby neurodegenerative disease, sustaining traffic along the ER's secretory pathway by preserving functional integrity of PDI [197].Nrf-2 also an important transcription factor, associated with the oxidoreductase system is also a crucial target to deal with. Naringin (4′,5,7-trihydroxy flavonone 7-rhamnoglucoside), the flavonone found in grapefruit and related citrus species has been found to upregulate the Nrf-2 and its consequent cytoprotective genes to act as a neuroprotective molecule [198]. Carnosine, an endogenous dipeptide biomolecule has been recently found to be a potent inhibitor of aging-induced increase in brain regional monoamine oxidase-A activity [26] and it can also reduce and restore the aging-induced deposition of amyloid-beta plaque quantitatively as well as qualitatively [199, 200]. Interestingly, the inhalation of patchouli oil (extracted from the leaf of *Pogostemon cablin*) has also the ability to modulate the blood platelet MAO-A activity and thereby in mood behavior [201].

6.2.8 Epigenetic modulations

Epigenetic markers such as histone deacetylases have been proved to be involved with AD. Treatment with HDACi (histone deacetylase inhibitors) such as sodium butyrate, phenylbutyrate, suberoylanilide hydroxamic acid, resveratrol induces

phosphorylation of tau protein, reduces the amyloidogenic processing of APP followed by restoration of learning and memory deficits in AD patients [202]. PD is also associated with epigenetic modulation. Where sporadic PD patients are linked with α-synuclein hypomethylation in dopaminergic neurons, the familial PD patients show a decrease in histone acetylation followed by an increase in α-synuclein levels [203]. α-synuclein-mediated neurotoxicity has been found to reduce by the treatment with Sirt2 siRNA [204]. A decrease in PD symptoms with the administration of dopamine may also be correlated with the deacetylation of histone H4 lysine 5 (H4K5), histone H4 lysine 12 (H4K12), and histone H4 lysine 16 (H4K16) [205].

7. Conclusion

The NDDs are progressive neuronal cell deaths due to environmental, biochemical, genetic and epigenetic factors. Generation of free radicals due to the oxidoreductase activity and deterioration of antioxidant system are found to trigger the aggregation of misfolded proteins in CNS causes mitochondrial dysfunctions and neuro-inflammations which finally leads to NDDs (**Figure 3**) [2]. Based on the predominant pathological features, NDDs can be classified in three different way, i.e. (a) anatomical, (b) the proteins undergoing conformational and biochemical modifications and (c) cellular pathology. Protein deposition pattern in CNS during NDDs are classified into several proteinopathies such as (a) cerebral amyloidoses, (b) tauopathies, (c) α-synucleinopathies, (d) prion diseases, (e) trinucleotide repeat diseases, (f) TDP-43 proteinopathies, (g) FUS/FET proteinopathies, (h) neuroserpinopathy, etc. depending upon the major protein aggregates [8, 44–46]. The diagnosis of neurodegenerative diseases is mostly associated with quantification of their specific receptor binding, changes in cellular metabolism or in anatomical structure. The neuroimaging techniques such as PET, SPECT, fMRI

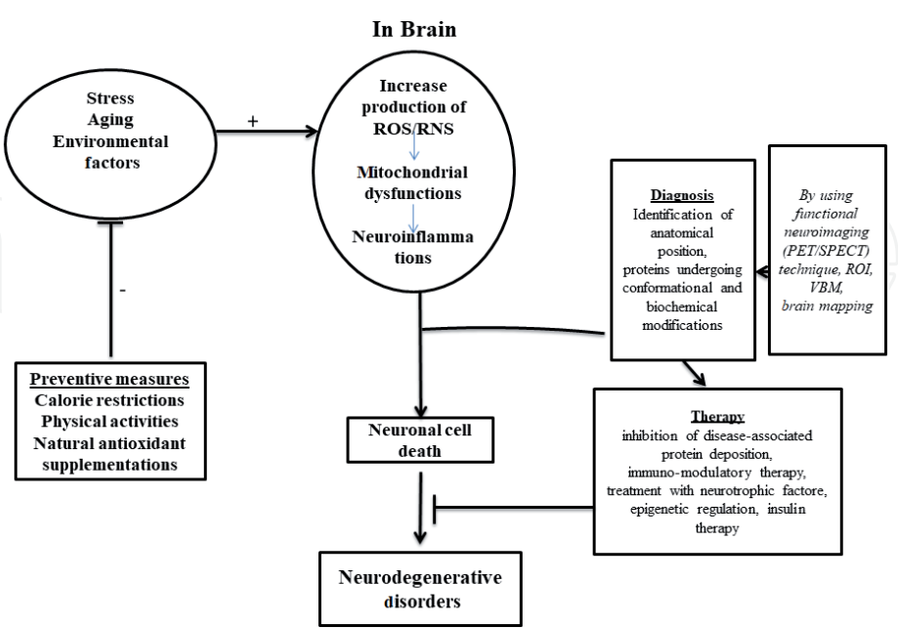

Figure 3.
Schematic representation of overall causes, diagnosis, prevention and therapy of NDDs.
The preventive measures are able to prevent the early causes of NDDs, while the diagnosis and therapy at later stage target and try to control the diseased condition due to NDDs. ROS: Reactive oxygen species; RNS: Reactive nitrogen species; PET: Positron emission tomography; SPECT: Single photon emission computed tomography; ROI: Region of interest; VBM: Voxel-based morphometry. + and - indicate activation and inhibition respectively.

etc. have been extensively used to diagnosed receptor activities and metabolic faith of damaged neuronal cells during diseased condition by using radio labeled tracers. Applications of metabolomics is another newer approach for the diagnosis and prognosis of NDDs. On the other hand, the characterization of brain regional anatomical changes in diseased conditions can be performed by brain mapping techniques. These advancements of technologies made the diagnosis of neurodegeneration much easier and an early diagnosis is also possible to some extent for most of the major NDDs. Although complete cure from NDDs/neurodegenerative disease(s) is not yet achieved but therapies that can prevent the early occurrence of NDDs are investigated. Individuals' deficits of vitamin B12, folate, and thyroid-stimulating hormones (TSH), cardio vascular and metabolic disorders, genetic and environmental factors are few of the reason behind NDDs and can be prevented by taking proper measure from the early life. Physical exercise, calorie restriction and few dietary components like DHA, polyphenols have neuroprotective effect and found to be beneficial for NDDs. Apart from prevention, there are limited medicated therapies are available in the market for the treatment of NDDs. But many strategies like inhibition of disease-associated protein deposition, immunomodulatory therapy, treatment with neurotrophic factor, epigenetic regulation, targeting oxidoreductases, and insulin therapy are under investigations and clinical trials. The current advancement in biochemical, pathological and pharmaceutical researches may ensure a better future of global neuronal health but it needs adaptation of a healthier lifestyle from the early day of life to avoid the occurrence of such NDDs.

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Conflict of interest

There is no conflict of interest to declare.

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