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Proteomics Analysis for Therapeutic Options of Neurodegeneration: A Review

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Abstract

Neurodegenerative diseases appear to share numerous common multifactorial degenerative processes that contribute to neuronal death, leading to functional impairments. Therefore researchers hope to understand the mechanisms of Neurodegenerative diseases in order to improve their chances of developing new therapies and strategies that may benefit patients. The Proteomics analysis is one of the strategies that researchers are focusing on in order to tackle such diseases as only through these analyses protein modifications can be characterized and be the targets of drugs that are identified. This review explores the various aspects associated with the neurodegenerative diseases and the recent proteomics analyses that may benefit their treatment. This review also strives to point out the literature hypothesized that oxidative modifications, mitochondrial dysfunction, and impairment of protein degradation execute neuron death. Numerous evidences present in literature raise the possibility the possibility that mitochondria and oxidative stress play a crucial role in neurodegeneration, opening new perspectives for therapy.

Keywords: Neurodegenerative disease; Biomarker; Proteomics; Mass spectrometry

Abbreviations: 2D-PAGE: Two Dimensional Polyacrylamide Gel Electrophoresis; α: Alpha; β: Beta; γ: Gamma; Aβ: Alpha Beta; AD: Alzheimer's Disease; ALS: Amyotrophic Lateral Sclerosis; ATP: Adenosine Triphosphate; APP: Amyloid beta Precursor Protein; CAG: Cytosine Adenine Guanine (Trinucleotides); CSF: Cerebrospinal Fluid; DJ-1: A Causative Gene for Familial PD and Oncogene; DS: Down Syndrome; EAD: Early Alzheimer's Disease; ESI: Electrospray Ionization; FTD: Frontotemporal Dementia; HTRA2: Mitochondrial Serine Protease; HD: Huntington's Disease; HNE: Protein-bound 4-hydroxy-2-nonenal; IT15: The Huntingtin Gene; LRRK2: Leucine-rich Repeat Kinase 2; MALDI-TOF-MS: Matrix-assisted Laser Desorption/Ionization Mass Spectrometry; MNs: Motor Neurons; MS: Mass Spectrometry; MS-MS: Tandem Mass Spectrometry; mtDNA: Mitochondrial DNA; NDD: Neurodegenerative Diseases; NTFs: Intraneuronal Neurofibrillary Tangles; REM: Rapid Eye Movement; RNS: Reactive Nitrogen Species; ROS: Reactive Oxygen Species; SOD2: Superoxide Dismutase 2; TDP-43: Transactive Response DNA-binding protein 43; p53: Tumor Protein; PARK2 and PARK6: Causative Genes for Familial PD and an Oncogene; PD: Parkinson's Disease; PKA: Protein Kinase A; PINK1: Putative Kinase 1; POLG: DNA polymerase γ; polyQ: Polyglutamine; PS1and PS2: Presenilin 1 and 2; PTMs: Post-translational Modifications

Introduction

The characterization and identification of putative disease modifying pathways in neurodegenerative disorders has enormous potential for discovery of new therapeutic agents that target these pathways. There is an increasing evidence that a number of potentially informative Neurodegenerative Disease (NDD) biomarkers can improve the accuracy of diagnosing NDD, especially when they are used as a panel of diagnostic assays and interpreted in the context of neuroimaging and clinical data [1,2]. The greatest contributing risk factor for NDDs is age. With an aging population, the inevitable result is a steep rise in the incidence of NDDs. The first publication that reported about Alzheimer disease (AD) was in 1907, which described a woman in her middle age that had lost her memory with a progressive loss of cognitive functions [3]. James Parkinson in 1817 was the first one who described medically a neurological syndrome and it was known as Parkinson's disease [4]. In 1912, the lewy body that characterized the Parkinson's disease was reported by Forman et al. [3]. Protein aggregation and inclusion body formation that was mostly associated with many forms of neurodegenerative diseases were detected using different techniques in the last century. These suggested that changes in physicochemical properties of the proteins in human brain were responsible for and lead to neurodegenerative diseases [5].

It is now possible to characterize brain cells, such as neurons and glial cells or even their subcellular components at the molecular level. This ability enables researchers to more closely examine brain cell and their molecular pathways to elucidate distinct brain functions. Proteomics allows the identification of thousands of proteins through descriptive and comparative analyses and can provide a detailed overview of a distinct cellular state. The advent of proteomics has allowed high-throughput screening methods to search for biomarkers that could lead to early diagnosis and treatment and to identify changes in the cellular proteome that could provide insight into disease etiology and possible treatments avenues [6]. In neurology and neuroscience, many applications of proteomics have involved neuro-toxicology and neuro-metabolism, as well as the determination of specific proteomic aspects of individual brain areas and body fluids in neurodegeneration. Investigation of brain protein groups in neurodegeneration such as enzymes, cytoskeleton proteins, chaperones, synaptosomal proteins and antioxidant proteins is in progress as phenotype related proteomics [7]. A biomarker is an analyst or a condition of the body that is measurable and is shown to be closely associated with the state of health. Biomarkers

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for neurodegenerative disorders are essential to facilitate disease diagnosis, ideally at early stages, monitor disease progression, and assess response to existing and future treatments. Biomarkers are broadly divided into three groups: physical measurements or phenotypes such as brain imaging, extracellular beta-amyloid (Aβ) plaque deposition [8]; DNA-based biomarkers [9]; and protein biomarkers [10].

Proteome analysis revealed perturbations in mitochondrial function, free radical production, and neurogenesis that were not observed in p53-deficient neurons. Changes in Tau, cofilin, and other proteins recapitulated abnormalities observed in neurodegenerative states *in vivo*. Additionally, DNA damage caused a p53-dependent decrease in expression of members of the Protein Kinase A (PKA) signaling pathway. PKA inhibition promoted death in the absence of DNA damage, revealing a novel mechanism by which endogenous down-regulation of PKA signaling may contribute to p53-dependent neuronal death [11]. This review will be vital in harnessing the wealth of existing data on neurodegenerative disease to develop an integrated understanding of its mechanisms and formulate optimal clinical guidelines. This review also focuses on the role of oxidative stress in neurodegenerative diseases. To aid the understanding of toxic targets in neurodegenerative diseases, this review includes characteristics, generation, regulation and physiological functions of Reactive oxygen species with their protein misfolding and aggregations.

Neurodegeneration and Neurodegenerative Diseases

Two words are combining the term “neurodegeneration”, "neuro," referring to nerve cells and "degeneration," referring to progressive damage. This term can be applied to several conditions that result in the loss of nerve structure and function. Kuldip [12] stated that the term neurodegeneration encompasses a broad range of diseases of central and peripheral nervous system. It is only seen in less than 5% of the cases as a clear genetic link have been established, however, majority is sporadic and driven by a combination of genetic and environmental factors. NDD which are incurable and debilitating conditions that result in progressive degeneration and/or death of nerve cells, primarily affect the neurons in the human brain include Alzheimer's disease (AD), Parkinson's disease (PD) which represents the second most common neurodegenerative diseases after AD, Huntington's disease (HD), Amyotrophic Lateral Sclerosis (ALS), and prion diseases. Human NDD range from rare to common illnesses. AD and PD pose serious public health challenges that will increase in the coming decades. Many discoveries have been made in the genetic causes and risk factors for several neurodegenerative diseases [13].

NDD are pathologies affecting body activities and functions (Figure 1) such as movement, balance, respiration and speech. Its incidence is increasing and becoming a threat of converting into a pandemic disease. Pal et al. [14] reported that, there is no treatment for these diseases because the neurons of the central nervous system cannot regenerate on their own after cell death or damage as well all of these diseases involve aggregation of protein or formation of inclusion body due to mutations in genes. The protein aggregation typically consists of fibers containing misfolded protein with a β-sheet conformation, Known as amyloid [5]. Recently, Pal et al. [14] stated that these diseases also cause problems related with movement or mental functioning and commonly characterized by the damage and lose of motor, sensory functions and associated cognitive and behavioral deficits. Numerous NDD were recorded and the most common are:

Alzheimer disease

AD is the most prevalent neurodegenerative disease, characterized by the presence of intraneuronal Neurofibrillary Tangles (NTFs) and β-amyloid-containing neurotic plaques as well as the loss of specific populations of neurons [15]. It is characterized by the extracellular deposition of Aβ fibrils and by the intraneuronal accumulation of abnormally phosphorylated tau protein. Preclinical AD can be diagnosed *in vivo* based on the presence of biomarkers [16,17], or post mortem by the presence of AD-type neuropathological alterations despite no signs of cognitive decline during life. According to Brookmeyer et al. [18] in many cases, Alzheimer may lead to Dementia and is expected to affect one in 85 people in the world by 2050. AD is mostly thought to be a disease in aging, with most diagnosis occurring in those aged 65 years and older [19]. However, early-onset cases do occur and typically arise from genetic causes [17].

Huntington's disease

HD is a devastating autosomal dominant neurodegenerative disease that results from a CAG trinucleotide repeat expansion within the disease-causing huntington/IT15 gene. HD, a neurodegenerative disorder characterized by cognitive and motor degeneration and is caused by an abnormal polyglutamine (polyQ) expansion in the N-terminal part of the huntingtin protein [20]. The clinical symptoms of HD are of progressive involuntary choreatic movements, bradykinesia, cognitive decline and psychiatric syndromes [21]. Impaired olfactory function was noticed in patients and presymptomatic gene carriers [22]. Aggregation of the mutant huntingtin proteins results in neuronal damage in the medium spiny neurons of the neostriatum and other neurons such as in the cortex [23]. Among several mechanisms, a recently suspected toxic mechanism is due to the presence of toxic oligomers [24].

Parkinson’s disease

PD is the second most common progressive neurodegenerative disorder. The neurological lesions are frequently accompanied by cytoplasmic inclusion bodies, termed Lewy bodies, which contains ubiquitin-positive protein aggregates [25]. The prevalence of Lewy bodies in PD has led to a central proposal that aberrant accumulation of protein aggregates is a key contributing factor to the development of Parkinsonism [25]. Loss of DAergic neurons in the substantia nigra of the midbrain and loss of other neurotransmitter phenotype neurons in other brain regions are characteristic neuropathological hallmarks [26]. Prominent clinical features of PD are motor symptoms (bradykinesia, tremor, rigidity and postural instability) and non-motor related PD symptoms (olfactory deficits, autonomic dysfunction, depression, cognitive deficits and sleep disorders). Non-DA brain regions that are affected in PD have recently attracted increasing interest because the onset of the non-motor symptoms linked to these neuropathological alterations are observed early in the course of the disease. They include Rapid Eye Movement (REM) sleep behavior disorder, subtle cognitive deficits, depression, olfactory dysfunction and constipation [27].

Amyotrophic lateral sclerosis

The term Amyotrophic Lateral Sclerosis (ALS) covers a spectrum of neurodegenerative syndromes characterized by progressive degeneration of motor neurons [28]. Rowland and Shneider [29] stated “Lateral sclerosis” which referred to the hardening of the anterior and lateral corticospinal tracts as Motor Neurons (MNs) in these areas degenerate and are replaced by gliosis. ALS, also known as Lou Gehrig’s disease and motor neuron disease, is a progressive, lethal,

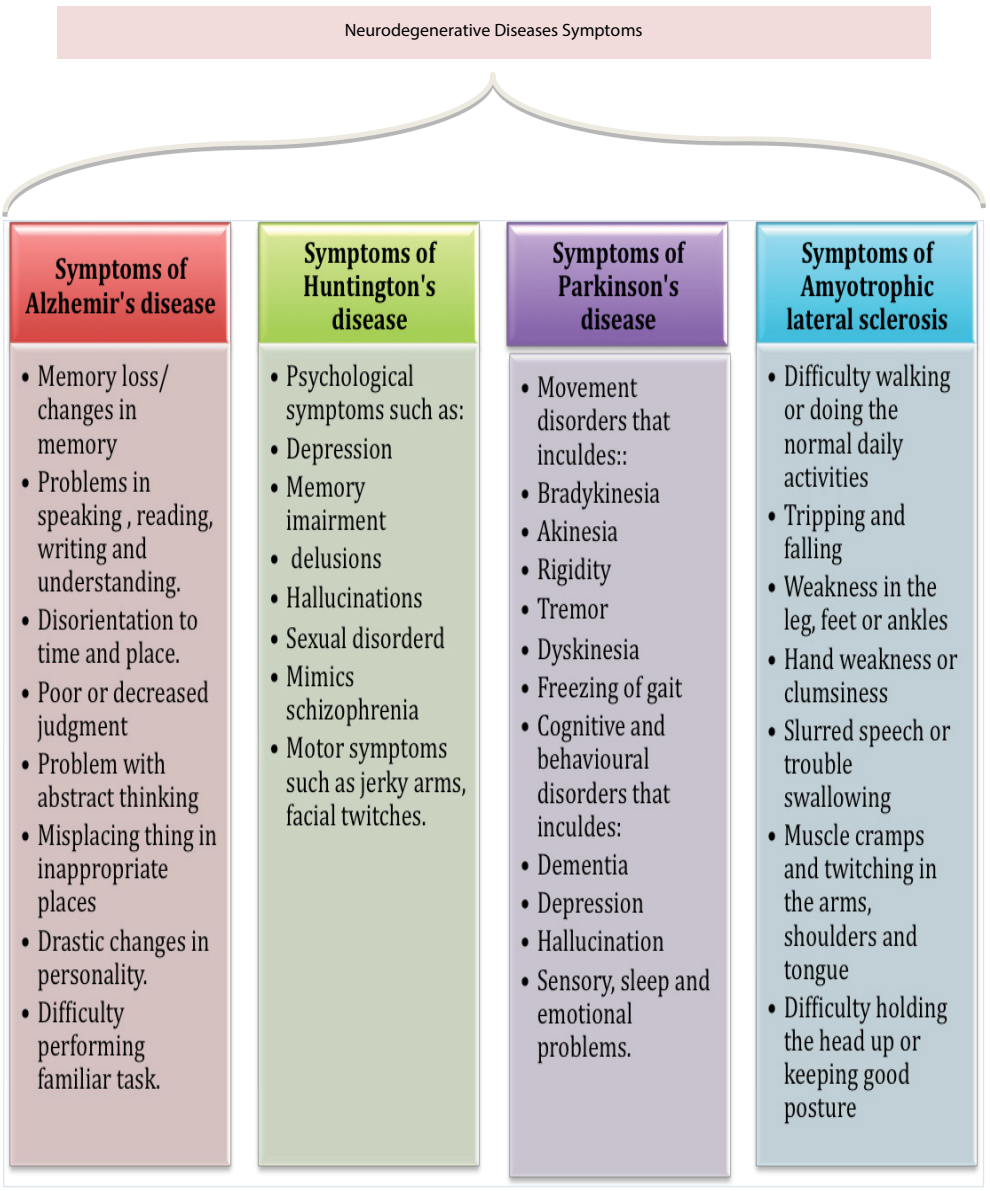

Figure 1: Symptoms summary of neurodegenerative diseases.

degenerative disorder of motor neurons. Mulder [30] mentioned that the hallmark of this disease was the selective death of motor neurons in the brain and spinal cord, leading to paralysis of voluntary muscles. The paralysis begins focally and disseminates in a pattern that suggests that degeneration is spreading among contiguous pools of motor neurons. One of the earliest symptoms of ALS may be the onset of distal weakness in the arms or legs, a lower motor neuron sign [31]. In the fingers and hands, the weakness presents as the inability to do fine motor movements, and it may be asymmetrical, affecting one arm and the opposite leg. It may also present as a one-sided weakness which then progresses to the opposite side. In contrast to motor weakness, cognitive function and hearing and visual capabilities are spared in the early stages of the disease [31].

Proteomics and neurodegeneration

The term "proteomics" was first introduced in the year 1955. It defines the entire protein complement of a cell line, tissue, or organism. Two definitions of proteomics were recently encountered. The first definition restricts its meaning to the large-scale analysis of gene products to studies involving only proteins [32]. As for the second definition, it combines protein studies with analyses that have a genetic readout such as mRNA analysis, genomics, and the yeast two-hybrid analysis. The proteomics analysis aims at obtaining a more global and integrated view of biology by studying all the proteins of a cell rather than each one individually. Mass spectrometry is considered an essential tool for proteomic analysis for identification and global semi-quantitative measurements of proteins as well as amino acids including protein-protein interaction, protein modifications, protein function, and protein localization studies [33]. Therefore, Verrastro et al. [34] studied and detected the amino acids (Figure 2) by proteomics using Mass Spectrometry. For many years, mass spectrometry has been used for detection and characterization of proteins, and is currently the most

useful method for determining oxidative damage of proteins [34].

The functions of proteomics are summarized as following [35,36]:

1. For the detection, identification, and characterization of the protein component of cells, tissues, and organs at any time point in both healthy and diseased.
2. For creating information related to protein expression levels, post-translational modifications (PTMs) and activity of protein, which plays an important role in understanding the biological system rather than just pure protein identification.
3. For systematic biochemical network analysis, employing mathematical modelling or other system biology tools.
4. For the identification of biomarkers and new targets for drug development.

The main goals of proteomics are to understand the molecular pathogenesis of neurodegenerative disorders, improving treatment efficacy, and enhancing the quality of information. So we need to determine the critical importance of molecular information derived from genomics and proteomics. Recently, proteomics analysis is trying to recognize new biomarkers that can be used for diagnosis and treatment of a specific neurodegenerative disease by using the protein spectrum in the biological material such as Cerebrospinal Fluid (CSF) [32]. Biomarker as a characteristic that is objectively measured and evaluated is an indicator of normal biological processes, pathogenic processes, or

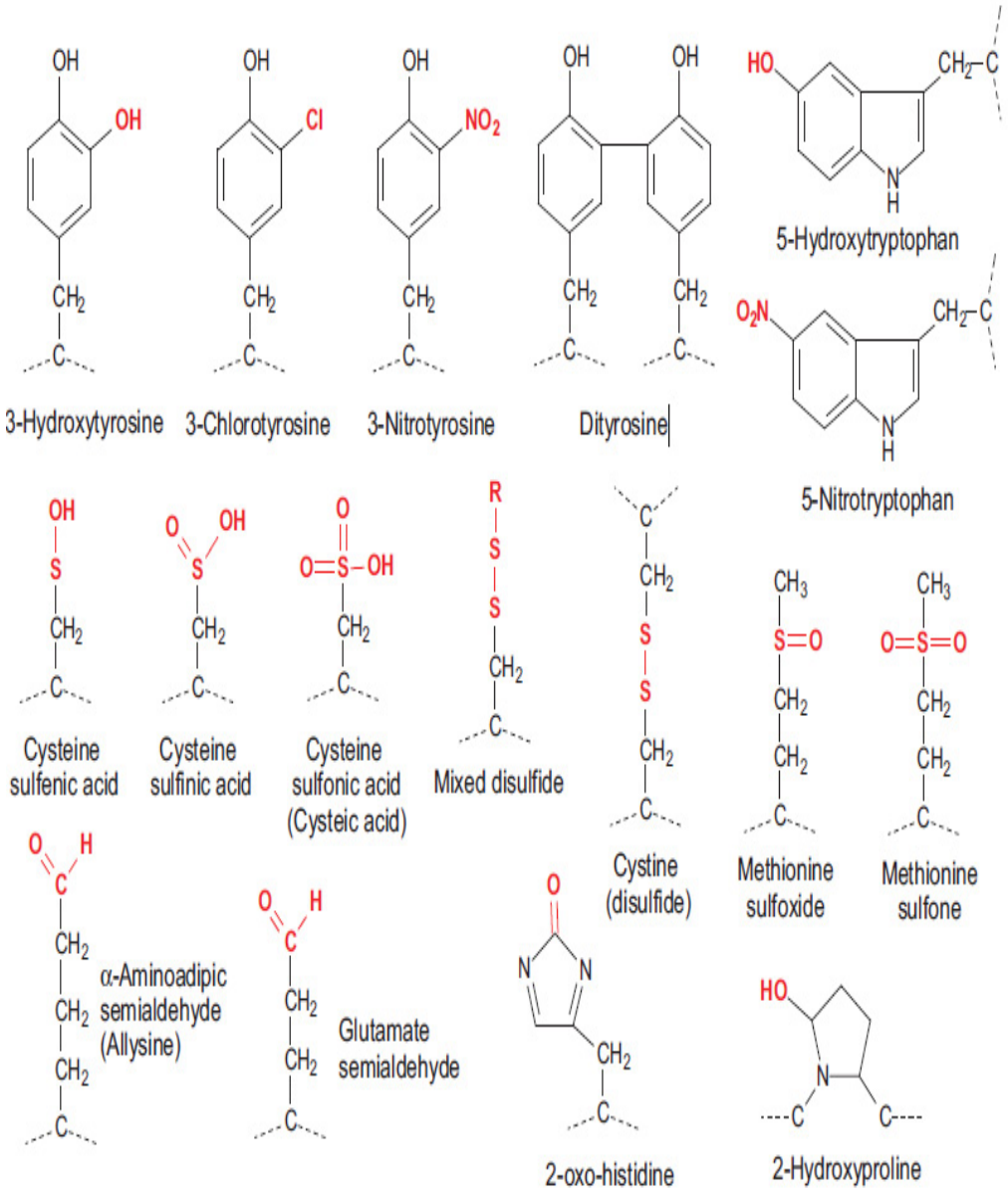

Figure 2: Amino acids detected by proteomics using mass spectrometry.

pharmacologic responses to a therapeutic intervention [37]. Therefore, biomarkers are powerful tools for assessment of neurodegenerative disorders development and extent of planned therapeutics in the management of the disease [36]. Analysis of CSF is an excellent source for identifying biomarkers for neurological diseases as it can be used in studying the biology of neurodegenerative diseases in living patients, and has been used as a major diagnostic tool for a wide range of conditions affecting both the central and the periphery nervous system [38]. By making a comparison between the protein content of CSF in disease and control groups, proteomics and computational software have emerged as a new and promising model for the discovery of new potential biomarkers, this area of research is however still challenging [33]. There are different proteomics techniques that have been used for the categorization of the human CSF proteome including the following:

1. Two dimensional polyacrylamide gel electrophoresis (2D-PAGE) which separates the proteins according to their charge and molecular weight. The limitation of using 2D-PAGE is that some proteins such as acidic/alkaline and hydrophobic proteins are hard to separate [36].

2. Mass Spectrometry (MS) is providing a useful technique for profiling the peptide or protein constituents of complex mixtures. MS also enables the assessment of qualitative and quantitative differences in protein profiles between different samples. There are many types of MS but the more common ones are Matrix-assisted Laser Desorption/Ionization Mass Spectrometry MALDI-TOF-MS and Electrospray Ionization (ESI) that could be used separately or together [14,33,36]. However, some common proteomic techniques use tandem MS (MS-MS) to analyze the small fragment ions of big ions whose mass was determined in the first MS dimension [36]. The mass spectrometry technique is considered as a sensitive and efficient method for protein identification. Henzel et al. were the first to develop the increased sensitivity of MALDI and demonstrate a fast peptide-mass-fingerprinting method for identifying proteins from two-dimensional gels [39]. The first step in MS technique is digestion of the complex mixture of proteins into small peptides with a protease, usually trypsin, which normally cleaves the protein on the C-terminal side of basic amino acid (lysine and arginine). The next step are separation of the peptides by reverse-phase liquid chromatography (LC) and analyzed by mass spectrometers such as quadrupole/time-of-flight (QTOF), ion trap (IT), orbitrap (OT), or ion cyclotron resonance (ICR) [40].

A proteomic biomarker is defined as 'a specific peptide/protein that is associated with a specific condition, such as the onset, the manifestation, or progression of a disease or a response to treatment' [41]. Proteomics biomarker discovery developed over ten years ago in neurodegeneration diseases such as AD, PD, and ALS, but more biomarkers for neurodegenerative disorders identification are needed. Six plasma biomarkers were identified in AD patients by plasma proteomic study using 2D-GE and LC/GC/MS, and one of them is α-1 antitrypsin, which has higher expression level using ELISA in plasma of AD patients [39-42].

Zetterberg et al. [43] have recorded around 30 CSF proteins which have been recognized in two or more proteomics studies as possible biomarkers for AD. In the same line, Korolainen et al. [44] listed 26 proteins which have statistical significant change in AD. 1D-PAGE beside 2D-PAGE with LC-MS/MS was used by Yin et al. [45] to identify a new biomarker in AD and they recognized 21 proteins that had different abundance between AD and controls. Also, 2D-PAGE is used to list other new biomarker for PD [45,46].

Besides using proteomics to discover new biomarkers in neurodegenerative diseases, proteomics are also used to investigate oxidative stress in the brain of patients of neurodegenerative diseases. Protein oxidation, lipid peroxidation (indexed by free or protein-bound 4-hydroxy-2-nonenal (HNE), and DNA and RNA oxidation (indexed by 8-hydroxy-2-deoxyguanosine and 8-hydroxyguanosine, respectively) are the main oxidative stress in the brain of AD [47]. Castegna et al. [48] used proteomics to determine protein oxidation in AD brain by using immunochemical assay of protein carbonyls coupling with two-dimensional polyacrylamide gel electrophoresis and mass spectrometry analysis. Moreover, Reed et al. [47] used 2D-PAGE and MS to examine lipid peroxidation in the early Alzheimer's disease EAD brain by protein-bound 4-hydroxy-2-nonenal (HNE) comparing to those in control. They have observed 20% increases in HNE-bound proteins in brain of subjects with EAD in contrast to control.

Neurodegenerative diseases causes

Oxidative stress and formation of free radicals/reactive oxygen species, mitochondrial dysfunctions, impaired bioenergetics and DNA damage, neuroinflammatory processes and disruption of cellular/axonal transport are linked to the formation of toxic forms of NDD-related proteins [49]. There are some proteins that are associated with most of the NDDs such as the microtubule-associated protein tau MAPT which is important for the assembly and stabilisation of microtubules, the Amyloid-β (Aβ), which is derived from the amyloid, the α-Synuclein which belongs to a family of abundant brain proteins, the Prion Protein (PrP), the Transactive response TAR DNA-binding protein 43 TDP-43. NDD-related proteins and their biochemical modifications can be used as biomarkers and may be targeted for the treatment of neurodegenerative diseases [50].

According to Saba et al. [51], there are different causes related to neurodegenerative diseases (Figure 3), most important to be discussed are specified below.

Abnormal protein dynamics with defective protein degradation and aggregation

Pathologically, the main causes of neurodegenerative diseases are the misfolding of the proteins and abnormal protein dynamics with defective protein degradation and aggregation [51], such as aggregation of amyloid-β (Aβ) in AD. The central role of proteins has been translated into biomarker research and also into development of novel therapeutic strategies. Indeed, vaccination against α-synuclein, amyloid-β (Aβ), or tau has been explored, in particular these proteins seem to propagate cell-to-cell and may be accessible to antibodies [52]. Cellular proteins should be maintaining their correct native three-dimensional conformations in order to be biochemically and functionally active. Misfolding, aggregation, and deposition make protein functionally inactive. Uttara et al. [53] showed that the toxicity of Aβ is attributed to histidine residues at position 6, 13 and 14. Those are structural sites for transition of metal ions (Cu^{2+}, $Zn^{2+}$and Fe^{3+}). According to Ramanan and Saykin [54], PD is characterized by deposition of inclusion bodies (Lewy bodies) of α-synuclein, huntingtin protein in HD, and transactive response DNA-binding protein 43 (TDP-43) in Front Temporal Dementia (FTD) and ALS.

Widespread application of specific antibodies against NDD-related proteins and their modifications led to an explosion of descriptions

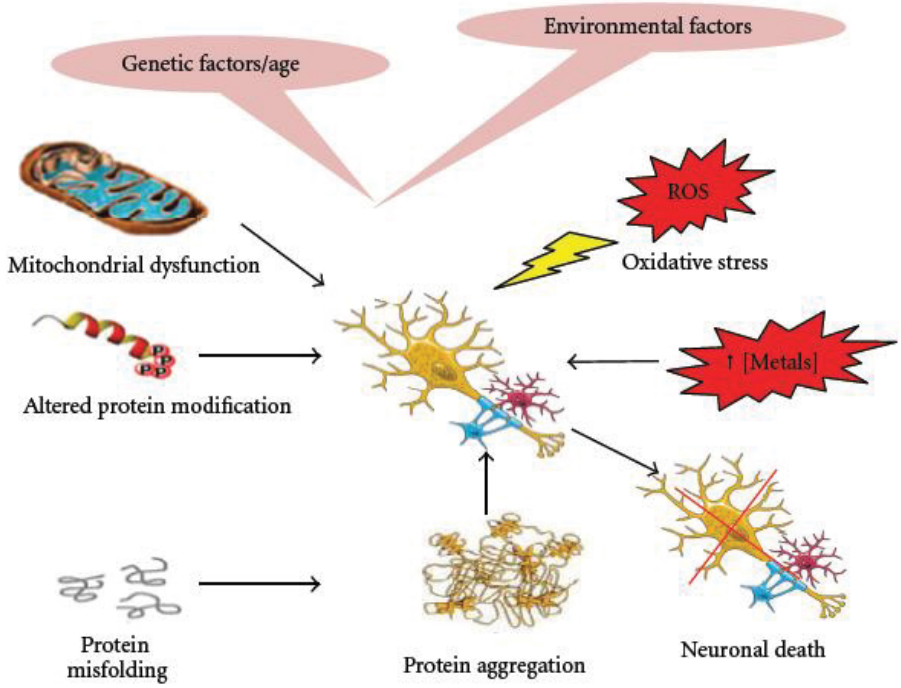

Figure 3: Different factors associated with neurodegenerative disease.

of new neuropathological phenotypes and enabled the development of reliable diagnostic criteria [55]. Numerous disorders are associated with the degeneration of neurons, including immunological disorders; furthermore, many gene alterations lead to the dysfunction of the encoded proteins. However, not all of these processes associated with microscopically detectable protein depositions, at least not with the currently applied techniques. For example, in hereditary spastic paraplegia, the neuropathological examination, without knowledge of the clinical symptoms, can suggest the condition but there are no specific protein inclusions that allow the observer to link the pathology to a specific gene mutation. Indeed, only few reports describe TDP-43, tau or crystalloid deposits in hereditary spastic paraplegia [55-57], but their detection is not enough to suggest the gene involved in the development of the disease.

Oxidative stress, free radical formation and mitochondrial dysfunction

Oxidative stress is having too several reactive species for available antioxidants, where oxidative damage is the biomolecular damage caused by attack of reactive species upon the constituents in living organisms [58]. Oxidative stress is a major mechanism by which many neurotoxins act. Animal studies using neurotoxicant-based models to reproduce the key features of neurodegenerative diseases have supported the general role of oxidative stress in neurodegeneration [59]. Free radical formation and protein oxidation in biological conditions represent a pathological event that is associated with many NDDs, such as ALS [60]. As well as the levels of nitrated oxidation proteins have been increased in AD brain and play a significant role in the pathogenesis of AD [56]. Many different reactive and oxidizing species, such as Reactive Oxygen Species (ROS) or reactive nitrogen species (RNS) associated with mitochondrial dysfunction, occur and differ in their reactivity to protein amino acids and sites [61]. Many brain functions were affected by ROS (Figure 4).

Lipid peroxidation, nitrotyrosine, reactive carbonyls, and nucleic acid oxidation are increased in vulnerable neurons of AD patients compared with control, regardless of whether individual neurons contain AD pathology [62]. Thus, signs of oxidative damage precede other pathological events in AD and considered as an early event in the disease pathogenesis [63]. Additionally, patients with prodromal AD, mild cognitive impairment, have increased levels of isoprostanes, which are products of polyunsaturated fatty acid oxidation [63].

Castegna et al. [48] stated that the more amino acidic targets for oxidation and free radicals formation are lysine, histidine, cysteine and methionine; however tyrosine is the generally nitrated amino acid. Many neurodegenerative diseases have an oxidative modification, which leads to oxidative damage to biomolecules, including proteins. Oxidative modification of proteins can have many side effects, such as damage of enzymatic activity, functional alterations, and damage of protein structure, which leads to protein aggregation. However, protein oxidation related neurodegeneration is not only caused by disturbed metal metabolism but also by genetic evidences; suggesting that persons associated with certain types of genetic mutations are more susceptible to neurological pathology compared to those with normal genetic profile [53].

Another major feature of neurodegenerative diseases is mitochondrial dysfunction. According to many researches, mitochondrial dysfunction may be an early or primary event in multiple neurodegenerative diseases. Mitochondrial dysfunction is a putative primary mechanism by which environmental toxicants may induce neurodegeneration [59]. In most of NDD, there are strong signs that explain the early occurrence of mitochondrial dysfunction

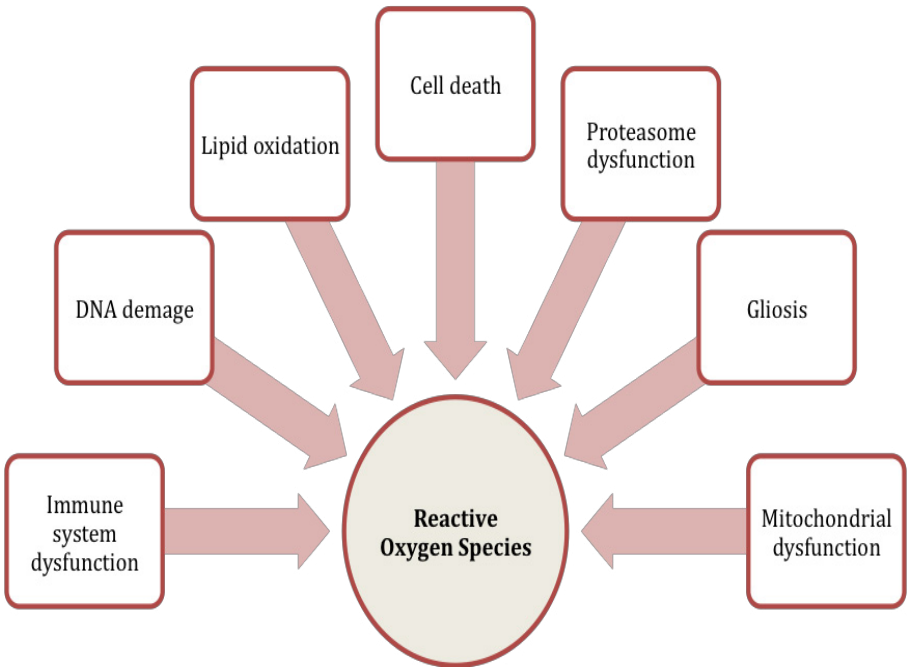

Figure 4: ROS effects over brain functions.

Disease	Genetic causes	Function
Alzheimer's disease	APP	Amyloid beta precursor protein. Gives rise to A β, the primary component of senile plaques
	PS1 and PS2	Presenilin 1 and 2. A component of γ-secretase, which cleaves APP to yield A β
Parkinson's disease	α-Synuclein	The primary component of Lewy bodies
	Parkin (*PARK2*)	An ubiquitin E3 ligase activity with an amino-terminal ubiquitin-like domain and a carboxyl-terminal ubiquitin ligase domain
	DJ-1	Protects the cell against oxidant-induced cell death
	PINK1 (*PARK6*)	A putative kinase 1 localized to mitochondria. Function unknown. Seems to protect against cell death
	LRRK2	A leucine-rich repeat kinase 2. Function unknown
	HTRA2	A Mitochondrial serine protease in the mitochondrial intermembrane space. Degrades denatured proteins within mitochondria. Degrades inhibitor of apoptosis proteins and promotes apoptosis if released into the cytosol
Amyotrophic Lateral Sclerosis	SOD1	Copper-zinc superoxide dismutase. Converts superoxide to hydrogen peroxide. Disease-causing mutations seem to confer a toxic gain of function
	TARDBP	The ubiquitin-positive neuronal inclusions protein and encoded by TDP-43.
	VCP	Valosin-containing protein
Huntington's disease	Huntingtin (*IT15*)	Function unknown. Disease-associated mutations produce expanded polyglutamine repeats

Table 1: Proteins function in neurodegenerative disorder with mitochondrial dysfunction. Republished and edited from Lin and Beal [64], with permission from right link/ nature publishing group.

in disease pathogenesis through the accumulation of mitochondrial DNA (mtDNA) mutations and net production of free oxygen species [64]. The mitochondrial dysfunction could also play a significant role in the pathogenesis of neurodegenerative disorder, and the evidence for mitochondria being a site of damage in these diseases is based in part on observed decrease in the respiratory chain complex activities in PD, AD, and HD [64,65]. Numerous studies [66-68] reported that mitochondrial accumulation of Aβ has been shown in AD patients. There have been several reports of mtDNA mutations in rare maternally inherited pedigrees of Parkinsonism, including the 12SrRNA gene in one family with Parkinsonism, deafness, and neuropathy [69]. More recently, mutations in DNA polymerase γ (POLG), a nuclear-encoded mitochondrial gene and multiple mitochondrial deletions, were reported in Parkinsonism associated with progressive external ophthalmoplegia [70]. The levels of the mitochondrial proteins prohibition, ATP synthase, and Superoxide Dismutase 2 (SOD2) are altered in the substantia nigra and frontal cortex tissue of PD patients compared to controls [71]. Chiasson et al. [72] performed proteomic studies in human brain tissue from PD patients and compared to those from healthy controls showed up-regulation of Peroxiredoxin II, mitochondrial Co-III, ATP synthase D chain, complexin I, profiling, L-type calcium channel d subunit, and fatty-acid binding protein.

Konstanze and Christian [73] indicated that several PD-associated genes interface with pathways regulating mitochondrial function, morphology, and dynamics. In fact, sporadic and familial PD seems to converge at the level of mitochondrial integrity. The mitochondrial complexes I, III, and V are defective in the cerebellar and brain regions of subjects affected by Down Syndrome (DS) [74]. Moreover, reduced mitochondrial redox activity and membrane potentials have been observed in DS astrocytes and neuronal cultures [75]. Exclusively, proteins and their function in main neurodegenerative disorder

with mitochondrial dysfunction are shown in Table 1 [64,76-80] and symptoms are shown in Figure 1 [81-83].

Conclusion

Diseases of neurodegenerative are complex, age-related disorders that are a growing health problem, exerting a tremendous burden on affected individuals. Today, more than ever, is an urgent need for new therapies to reverse the progression of these disorders. Up to now, many cellular and molecular events contributing to these disorders have been revealed. Furthermore, increasing evidence implies that mechanisms underlying neuronal demise in these disorders may be shared. As the compromised mitochondria function, misfolding of proteins has also been reported in many disorders. Finally, diagnosis and therapy of complex neurodegenerative diseases requires novel molecular targets. Neurodegenerative disease diagnosis and treatment strategies may need to evolve to reflect a complex genetic architecture. A combination of clinical biomarkers including genotype and blood analysis, brain imaging, and medical history data might be required in order to estimate the effects of multiple pathways.

Acknowledgment

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