Review Article

Mechanism and biomarkers for neurodegenerative diseases: A systematic review

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ABSTRACT

Neurodegenerative disease such as Parkinson's disease (PD), Alzheimer's disease (AD), Multiple sclerosis (MS), Huntington's disease (HD) are characterized by progressive loss of cognitive function, dementia and problems with movement. Neuronal loss is associated with extra and intercellular accumulation of misfolding proteins, oxidative stress, free radical formation, mitochondrial dysfunction, disruption of neuronal golgi apparatus, impaired bioenergetics, dysfunction of neurotrophins.

Biomarkers that might aid in the diagnosis of these devastating and globally important disease are urgently sought and required. Therefore, range of biomarkers are explained for neurodegenerative disease.

1. Introduction

Neurodegenerative disorders (NDD) comprise a lot of obsessive conditions beginning from moderate dynamic and irreversible brokenness and loss of neurons and neurotransmitters in selected regions of the sensory system which decide clinical introduction and course. The significant fundamental mechanisms prompting neurodegeneration (ND) are viewed as multifactorial brought about by hereditary, ecological and endogenous elements identified with aging.[1] Neurodegenerative illnesses speak to a significant risk to human wellbeing. These age-subordinate issue are getting progressively predominant, to some degree in light of the fact that the older population has expanded lately. Instances of neurodegenerative diseases are Alzheimer's disease, Parkinson's disease, Huntington's infection, amyotrophic lateral sclerosis, frontotemporal dementia and the spinocerebellar ataxias.[2] Patients with these disease show genuine neurological incapacities, for example, memory debilitation and motor problems, for which there are no cure.[3] Most of procedures include unusual protein elements because of insufficiency of the ubiquitin–proteosome–autophagy system, oxidative stress and free radical reaction, hindered bioenergetics, dysfunction of neurotrophins, mitochondrial dysfunction, 'neuroinflammatory' processes and interruptions of neuronal golgi complex and axonal transport.[1]

These days, symptomatic medicines exist, however there are as of now no compelling medications to invert or stop the movement of the illnesses. Improving the early and predictive analysis of neurodegenerative sicknesses is the vital significance and tremendous efforts are in progress. In this way, it is required a tool to help doctors, epidemiologists, and researchers in the investigation of human diseases by confirming a diagnosus and following ailment movement, which may distinguish explicit remedial targets.[4] A biomarker is a research center estimation that recognizes a disease or mirrors the movement of an illness process[5]. Along these lines, improvement of biomarkers may quantify disease risk, presence, and progression is one of the principle objectives and challenges in explore of neurodegenerative diseases.[4]

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1.1. Mechanism of neurodegeneration

NDDs presently are characterized by known hereditary systems and additionally to the significant components of their protein stores. In view of basic conformational changes of proteins, these disorders are indicated as 'protein misfolding' or proteinopathies.[5,6]

1.2. Mitochondrial dysfunction and reactive oxygen species (ROS) production

Neurons in the human cerebrum have gigantic oxygen utilization and metabolic rates. Consequently, neurons depend on mitochondria that are found in abundance in cerebrum tissues for the creation of vitality by oxidative phosphorylation. Mitochondria are the focal sites of ROS, as regular side effects of the oxidative phosphorylation cascade, and extreme production of ROS is generally counterbalanced by the typical homeostasis function of mitochondria. Amyloid beta (Aβ) shows up as a single particle however will in general structure little groups that are soluble and ready to travel unreservedly in the brain and inevitably frames plaques that are signs of Neurodegeneration.[7] Mitochondrial related amyloid precursor protein (APP) structures a complex with the translocase of the outer mitochondrial membrane40 (TOM40) import channel and the translocase of the inner mitochondrial membrane 23 (TIM23) import channel and causes the block of nuclear encoded cytochrome c oxidase subunits IV and Vb proteins. Following this occasion, cytochrome c oxidase action is diminished and the generation of hydrogen peroxide is expanded in mitochondria. This discovering corresponded with a more elevated level of regional dissemination of mitochondrial APP in Neurodegeneration-vulnerable areas, including the frontal cortex, hippocampus, and amygdala. The mitochondrial aggregated Aβ actuates mitochondrial damage and neuronal death.[8]

1.3. Protein Oxidation

There is tremendously collected proof that ROS might be key to the pathogenesis of neurodegeneration in Alzheimer's disease (AD). The ceaseless develop of ROS and RNS (receptive nitrogen species) prompts protein oxidation and lipid peroxidation. Protein oxidation in cell is reflected by the expanded degrees of protein carbonyls and 3-nitrotyrosine (3-NT). Protein carbonyls can be produced by the response of the superoxide anion, which prompts the discontinuity of the protein backbone. In addition, protein carbonyls may likewise be produced by hydrogen atom abstraction and the particular assault of ROS on a few amino acid side chains, for example, lysine, arginine, and proline. ROS assult on protein structure may bring about the arrangement of Michael adducts between histidine, cystine and lysine, buildups and the glycoxidation of lysine amino groups, which make advance glycation end products (AGEs).[9] Some biochemical changes exist in proteins that play straightforwardly or by implication in mitochondrial energy metabolism, for example, triosephosphate isomerase, α-ATPase glyceraldehyde 3-phosphate dehydrogenase, creatine kinase and phosphoglycerate mutase 1. The oxidation of these vital enzymes caused a reduction in ATP generation keep up the ordinary digestion and elements of neuronal cells, which brought about the perturbation of ion pump and potential gradients. Furthermore, ATP deprivation in synapses can cause an unusual phosphorylation of tau protein, which can advance to Neurodegenerative disease onset.[10]

1.4. Lipid Peroxidation

Lipid peroxidation refers to oxidative degradation of lipid particles. It is a chain reaction whereby a H atom is abstracted from lipids in cell layers by free radical species, bringing about cell membrane damage. The cerebrum is viewed as vulnerable against lipid peroxidation because of its high oxygen utilization, elevated level of redox metal ions, diminished antioxidant defence mechanism, and significant level of polyunsaturated fatty acids (PUFAs). The toxic response between free radicals and phospholipid-bound arachidonic acid in cell layer delivers free 4-hydroxy-2-trans-nonenal (HNE),acrolein, neuroprostanes, and isoprostanes.[11] The aldehydic result of lipid peroxidation HNE is profoundly harmful and can frame covalent bonds with proteins through Michael adduction to amino acid cysteines, lysines and histidines. Raised degrees of HNE-histidine Michael adducts in the AD hippocampus and the covalent adjustment of the histidine side chain of Aβ brings about an increased accumulation of this tau protein. The collection of Aβ in mitochondrial membranes causes modifications and expanded permeability in the membrane, which prompts the leakage of cytochrome c and the useful variation from the norm of the electron transport chain, which finishes in cell apoptosis. Lipid peroxidation and Aβ generation in neuronal cells are capable for prompting c-Jun N-terminal kinase (JNK) pathways, leading to programmed neuronal death.[12]

Nitrosative Stress[7]

Nitrosative stress is a condition whereby Reactive Nitrogen Species (RNS) generation isn't counteracted a variety of guard systems and makes damage to the intracellular segments of cells. Nitric oxide (NO), the significant patron of RNS, works as signaling molecule in controlling neural development, neurotransmitter release, and synaptic versatility. Nitrosative pressure has been involved in marked cognitive impairment that is related with synaptic dysfunction and glial activation. However, nitric oxide delivered because of Aβ in AD has been found to initiate mitochondrial fission through the S-nitrosylation of

dynamin-related protein 1 (SNO-Drp1), causing synaptic hindrance and neuronal damage.

Excitotoxicity:[13]

Excitotoxicity assumes a key role in intoxication of certain poisons like domoic acid (Amnesic shellfish poison by marine algae), kainic acid, and so on. Excitotoxicity is the neurotic procedure by which nerve cells are damaged and killed by over the top glutamate stimulation. Excitotoxicity may likewise express in various neurotic conditions like, spinal cord damage, horrendous brain damage, multiple sclerosis, stroke, amyotrophic lateral sclerosis, and other neuronal issue. It is additionally engaged with most parts of typical brain capacities including perception, memory, and learning. Excitotoxicity can happen through over-initiation of the NMDA receptor with the ensuing convergence of Ca2+, activation of both clamor and inducible nitric oxide synthase (iNOS), and abundance generation of nitric oxide.

2. Biomarkers

The expression "biomarker", a portmanteau of "biological marker", alludes to a general subcategory of therapeutic signs – that is, target signs of medicinal state observed from outside the patient – which can be estimated precisely and reproducibly. Restorative signs remain as opposed to medicinal side effects, which are constrained to those signs of wellbeing or ailment saw by patients themselves.[14]

The utilization of biomarkers in essential and clinical research just as in clinical practice has become so regular spot that their essence as essential endpoints in clinical trials is currently acknowledged nearly without question.[15] The present day biomarker research and development of novel methodology have developed dependent on the essential role of proteins. Biomarkers can help in the advancement of medication discovery by giving an early comprehension of the disease and even in picking the potential remedial objective which may treat or restrain the disease progression.[15]

There are a couple of biochemical strategies that have been institutionalized for neurotoxicity testing. These might be ordered into 3 groups

1. Biomarkers of exposure
2. Biomarkers of effect
3. Biomarkers of susceptibility.[16]

General Mechanism[16]

DNA might be utilized as a file for cell multiplication and cell number in nervous tissues. For instance in the assessment of the impact of lead during early development, there is a decrease in brain weight and a reduction in total brain protein without an adjustment in the number of brain cells. Early activity of lethal specialists might be showed as an unsettling influence of the DNA enzyme repair system. This might be auxiliary to impedance with

brain zinc level by for instance lead (Pb). Synthetic substances may cooperate with the DNA molecule either by straightforwardly authoritative to the nucleic acid moiety or to its related chromosomal proteins. Such changes in DNA molecules typically meddle with its function, and these might be utilized for examining neurotoxicity.

Numerous neurotoxic agents have been appeared to adjust the pivot rate and thusly the metabolic half existence of the neurotransmitters. Changes in brain catecholamine focuses have been embroiled in the neurotoxicity of carbondisulphide as it increased dopamine and diminished norepinephrine concentration by hindering dopamine β hydroxylase. Organophosphorus compound insecticides apply their intense impact by inhibition of acetylcholinesterase that prompts collection of acetylcholine at receptors in both the central and peripheral nervous systems. Lead, the chlorinated hydrocarbons, chlordecone and a few others have all been appeared to meddle with neurotransmitter take-up process. Along these lines their assessment may fill in as biomarkers of neurotoxicity.

A basic regular spot biomarker of neurotoxicity of both susceptibility and impact is calcium. Influx of Ca^{++} upon depolarization of the nerve endings triggers the arrival of neurotransmitters from synaptic endings. Lead and manganese have all been accounted for to meddle with calcium-dependent neurotransmitter discharge. Ion channels control numerous neuronal capacity. Along these lines annoyance of these channels might be reflected by variation in ion levels. A notable one is K+. The Na+/K+ ATPase pump is required for maintaining Na+/K+ concentrations. The pump might be repressed by some toxicants, for example, tetrodotoxin and saxitoxin. This is the mechanism of toxicity of the peptide toxin, scorpion poison which has recently been appeared to have K+ channel affinity.

Clearly the biochemical tests currently called markers can assume a significant role in recognizing, foreseeing and screening for neurotoxicity.

Types of biomarkers[15]

2.1. Davis and associates arranged biomarkers into 6 classes

1. Biomarkers of risk
2. Diagnostic biomarkers reveals the presence of a disease
3. State biomarkers, a quantifiable qualities that mirrors the reality of a particular disease process
4. Stage biomarkers reflects extant classification of staging that categorize present phase of disease of an individual
5. Treatment reaction biomarkers records the probability of reaction to a given treatment

2.2. Prognostic biomarkers would foresee the presumable course and result of an ailment.

Alzheimer's Disease[7]

Alzheimer's disease (AD) one of the most widely recognized neurodegenerative ailments that influence a large population around the world.

Alzheimer's disease is described by the strange gathering of extracellular amyloid-β plaques and intraneuronal neurofibrillary tangles in brain locales and shows as a kind of dementia in matured people that outcomes in memory misfortune, multiple cognitive abnormalities, and intellectual disabilities that meddle with quality of life.

3. Biomarkers for alzheimer's disease

3.1. Beta Amyloid[17]

Beta amyloid 1-42 is the traditional marker of amyloid pathology in the brain. Patients with AD show a significantly diminished degree of beta amyloid 1-42 which is distinguishable effectively 5 to 10 years before the beginning of psychological changes. Interestingly, beta amyloid 1-40 stays unaltered in AD patients and gives a marker of the individual amyloid level. The most dependable proportion of amyloid pathology is given by the proportion of beta amyloid 1-42 to 1-40, as it considers the patient's individual amyloid synthesis. A proportion of under 0.1 shows amyloid pathology. By assessing just beta amyloid 1-42 the patient can't be effectively classified. In any case, with the proportion of beta amyloid 1-42 to 1-40 the patient can be definitively analyzed. Further examinations have exhibited that the beta amyloid 1-42 to 1-40 proportion gives a higher scientific strength than beta amyloid 1-42 alone with respect to variables, for example, the material of the sample collection tube or the quantity of sample freeze-thaw cycles. The beta amyloid 1-42 to 1-40 proportion additionally yields a higher relationship to positron emission tomography (PET) imaging than beta amyloid 1-42 alone (93% compared to 83%).

Total Tau Protein[15]

The microtubule-related tau protein is the significant constituent concerning to intraneuronal change. At the point when tau protein is discharge from the binding site can shape anomalous aggregates. At the molecular level, the tau pathology observed in AD patients vary despite the fact that tau pathology has been seen in different other neurological issue. Under the speculation that tau protein is discharged extracellularly because of neurodegeneration process, tau protein was evaluated in the Cerebro spinal fluid (CSF). Studies have shown an increase in complete tau concentration in Alzheimer's disease when contrasted with nondemented aged subjects and with age the convergence of total tau increments deliberately.

3.2. Hyper Phosphorylated Tau Protein

The principal techniques that shows the hyperphosphorylated tau protein concentration in cerebro spinal fluid were distributed in 1999. In AD about 30 phosphorylation epitopes have been recognized. Hyperphosphorylated tau protein has been grouped into three subtypes in particular: P-tau231p, p-tau181p and p-tau199p. Increased CSF concentration of P-tau have been found in AD patients.[18] In an examination that include around 2000 patients and controls have indicated distinction between the subtypes in recognizing the AD patients from the control subjects and furthermore from various types of dementia, p-tau231p and p-tau 181p shows preferable outcomes over p-tau199p.[19]

3.3. Parkinson's Disease[20]

Parkinson's disease (PD) is an age related neurodegenerative disease portrayed by dopaminergic neuron misfortune in the substantia nigra standards compacta prompting progressive motor disability.

Biomarkers for parkinson's disease:

3.3.1. α-Synuclein

α-synuclein is an individual from synuclein group of protein, which likewise incorporates β and γ-synuclein. The non-Aβ part of Alzheimer's disease (NAC) are the unknown proteins present in the structure of α-synuclein which gives it a one of a kind trademark when contrasted with different individuals from the family. Different examinations have depicted that a large portion of the PD cases are occasional and uncommon familial structures including transformations of genes.[21] Mutation in the α-synuclein gene have been related to the general risk factor for PD. In post-mortem brain tissue samples from PD patients, Lewy bodies are a marker of the disease pathology, regardless of whether patient convey α-synuclein hereditary transformations. For the finding of the illness movement, checking α-synuclein in the blood and cerebrospinal fluid might be useful.[22]

3.3.2. DJ-1[23]

Mutation of DJ-1 has an extremely less role in the reason for parkinsonism anyway modified degrees of DJ-1 in plasma might be useful in recognizing PD patients and healthy people. Neuroimaging of the dopamine system is the benchmark biomarker for PD. In clinical research biomarkers are utilized as a devices to give early biological readouts in trials of new therapeutics. Expanded oxidative pressure and neuroinflammation are related with PD. Convergence of 8-OHDG, an oxidative pressure marker is seen as higher in the cerebrospinal fluid of patients with the disease when contrasted with healthy subjects.

Motor Neuron Disease (MND)[24]

MND are uncommon however decimating ailments described by degeneration of the upper and lower motor neurons. The most incessant structure is amyotropic lateral sclerosis (ALS), otherwise called Lou Gehring syndrome, which has a prevalence of 2 out of 100,000 people. Damage happens directly to the axons, and signs incorporate muscle weakness, cramps in the arms and legs, dysphagia and dysarthria. As the disease advances, side effects spread and turn out to be increasingly exceptional, finally prompting total loss of autonomy and capacity to communicate.

3.4. Biomarker for motor neuron disease[24]

3.5. Neurofilament

A best in class biomarker for MND is neurofilament, which shows an expanded level in MND, particularly in ALS. Assurance of neurofilament in CSF is useful for determination of MND and separation from MND mimics, for example, polyneuropathy, myopathy and sporadic inclusion body myositis. Parameters which are applicable for diagnostics are the phosphorylated neurofilament heavy (pNf-H) and the neurofilament light (Nf-L) subunits. Nf-L can separate MND from AD, though the markers T-tau and P-tau were not ready to accomplish this qualification. Neurofilament is right now at the passage among research and routine diagnostics and will before long be added to symptomatic guidelines for MND. It is foreseen that standard assurance of neurofilament will empower quicker finding of MND and may also demonstrate helpful for anticipation.

3.6. Huntington's Disease[25]

Huntington's disease (HD) is an autosomal predominant, neurodegenerative disorder, ordinarily introducing in youthful middle age. It is portrayed by noticeable psychiatric problems, just as dynamic deterioration in both cognitive capacity and motor control, prompting an early demise.

3.7. Biomarkers for huntington's disease

3.7.1. Endocrine biomarkers
Hypothalamic dysfunction serves to be one among the significant reason for misfortune in weight, despondency, upset sleep cycle in beginning times of HD.[26] With the headway of disease in HD patients increase in urine cortisol levels was evident. To follow disease, recognizing the adjustments in endocrine are of energy as biomarkers of HD.[27]

3.7.2. Oxidative stress biomarker
In HD patients, mitochondrial dysfunction has been observed and in pre-symptomatic HD gene carriers in pre-symptomatic HD.[28] Mutant huntingtin and its cleavage items are being researched as potential biomarkers as the prompt reason for neuronal dysfunction and demise in HD.[29]

Biofluid Biomarkers[30]

Biofluid biomarkers are so called because they are quantified in body fluids, ideally with minimal invasiveness, good accuracy and high discriminatory power. They spread not just the most normally utilized fluids, for example, blood and urine, yet in addition cerebrospinal fluid (CSF), saliva, and sweat, among others. Biofluid biomarkers have the intrigue of being fit for exact, dependable measurement, frequently in mass or often in bulk. However, a solitary example can create results for numerous analytes of interest.

4. Conclusion

The review summarized the concept of neurodegenerative disease along with working definition, a conceptual framework to understand mechanism of different neurodegenerative disease. Biomarkers for a neurodegenerative disease should reflect the central pathogenic processes of the disease. Identification of biomarkers plays important role in advancement of drug discovery and development, increase efficiency and accuracy of diagnosis and treatment.

It is important to emphasis the evidence of new biomarkers for neurodegenerative disease that can be used to predict, detect and monitoring neurotoxicity could prove preclinical, nonclinical and clinical decision making.

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