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Review Article

Biomarkers in Neurodegenerative Diseases

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Abstract

Biomarkers also referred as natural markers function as therapeutic indications of a medical state. Assessment of biomarkers puts forth a clear picture regarding the risk, seriousness and stage of the disease while also helps in prognosis, diagnosis and designing the treatment for the specific illness. The present day biomarker research and development of novel therapeutic approach have emerged based on the primary role of proteins. Biomarkers can help in the advancement of drug discovery by providing an early understanding of the disease and even in choosing the potential therapeutic target which may treat or inhibit the disease progression. In this review we describe about the various biomarkers that are involved in the above mentioned neurodegenerative diseases and their role in the pathogenesis of the disease.

Keywords: *Biomarker; Neurodegenerative Disorders; Pathogenesis*

Introduction

The term 'biomarkers', also known as "natural marker", alludes to a wide variety of therapeutic indications - target signs of medicinal state detected from outside the patient - which can be estimated precisely and reproducibly. National Institutes of Health has defined it as a distinguishing property which is accurately measured and estimated as a sign of normal biological functions, pathogenic processes, or pharmacologic responses to a therapeutic intervention [1]. A joint project on substance safety, the International Program on Chemical Safety, drove by the World Health Organization (WHO) and as a team with the United Nations and the International Labour Organization, has characterized a biomarker as "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease." Biomarker estimations can help clarify empirical results of clinical trials by relating the impacts of interventions on molecular and cellular pathways to clinical responses. In doing as such, biomarkers provide a tool for the researchers to gain a mechanistic understanding of the distinction in clinical response that might be affected by uncontrolled factors [1]. Biomarkers can help in expediting the drug discovery process for a particular disease by providing an early insights of the disease [2]. Biomarkers that provide the physiological or pharmacological information about the disease can be used to choose a potential therapeutic target which may treat or inhibit the disease progression [3]. There are a large number of methods available to obtain an information about the conditions of the brain in both healthy as well as in a diseased condition. These include estimation of blood or cerebrospinal fluid or using brain imaging can be used to measure any change in the neuronal plasticity and its functions [4].

Types of Biomarkers

Davis and colleagues classified biomarkers into 6 categories: (i) biomarkers of risk (ii) diagnostic biomarkers reveals the existence of a disease (iii) state biomarkers, a quantifiable characteristics that reflects the seriousness of a specific disease process (iv) stage biomarkers reflects extant classification of staging that categorize present stage of illness of an individual (v) treatment response biomarkers records the possibility of response to a given treatment (vi) Prognostic biomarkers would predict the likely course and outcome of an illness [5]. Numerous neurodegenerative diseases are classified depending on either histological findings or based on standardized clinical criteria. Biomarkers can possibly recognize neurodegenerative diseases at an early stage, by which it helps in introducing techniques to standardised classification of a disease, and expands the knowledgebase regarding the core pathogenesis of the disease [4].

Neurodegenerative diseases

Neurodegeneration is defined as the loss of functional neurons with consequent clinical deficit [6]. Neurodegenerative diseases represents an extensive group of neurological disorders with heterogeneous clinical and pathological expressions influencing particular subsets of neurons in specific functional anatomic systems; they emerge from for unknown reasons and progress in a relentless manner [7]. Neurodegenerative diseases like Alzheimer's disease (AD), Parkinson disease (PD), Multiple sclerosis (MS), Huntington's disease (HD) are a heterogeneous group of disorder characterized by a progressive or selective loss of functional neurons [8].

Mainly, there are two different pharmacological approaches to address neurodegenerative diseases. Symptomatic treatment aims to moderate impaired function of the already damaged neurons, for instance, by modifying the activity of NMDA receptors, or by expanding the neurotransmitter levels trying to compensate for ongoing damage. Conversely, disease modification approaches aims to counteract further progression or even reverse the course of a disease [6]. Various ground-breaking studies proved that most of the neurodegenerative diseases are characterized by protein deposition with altered physicochemical properties which are also referred as misfolded proteins [9]. There has been reports which relates microglial activation, reactive oxygen species and neuroinflammation in the human brain responsible for neurodegenerative diseases [10]. Toxic forms of neurodegenerative diseases related proteins are formed due to formation of free radicals or reactive oxygen species and oxidative stress, impaired bioenergetics and DNA damage, mitochondrial dysfunctions, disruption of cellular/axonal transport and neuroinflammation [11]. The roots of present day biomarker research and development of novel therapeutic approach have emerged based on the primary role of proteins [12].

Alzheimer's Disease

Alzheimer's disease is one of the most common neurodegenerative disease [13]. The major pathological lesions is due to the accumulation of insoluble filamentous aggregates known as amyloid [14]. The symptoms of AD include loss of memory, cognitive dysfunction, motor impairment and psychiatric symptoms. Three biomarkers such as amyloid beta, total tau protein and hyperphosphorylated tau that are obtain from cerebrospinal fluid (CSF) are established for diagnosis of AD [15].

Amyloid β

Amyloid plaques are a histopathological characteristics of AD and the aggregated Aβ of which the plaques are formed plays an important role in the pathogenesis of the disease. Aggregated amyloid is toxic to neurons as they may act synergistically with neurofibrillary tangles pathology has been evident in neuronal culture and in mouse models [14]. Various observations has led to the hypothesis that increased production, aggregation and accumulation of Aβ fibrils leads to senile plaques, neurotoxicity and clinical symptoms of AD [16]. Deposition of Amyloid beta plaque with a length of 42 amino acids is used to characterize AD [13].

Total tau protein

The microtubule-associated tau protein is the major constituent concerning to intraneuronal change in AD patients [17]. When tau-protein is release from the binding site can form abnormal aggregates. At the molecular level, the tau pathology observed in AD patients differ although tau pathology has been observed in various other neurological disorders [18]. Under the hypothesis that tau protein is released extracellularly as a result of neurodegeneration process, tau protein was quantified in the CSF [13]. Studies have demonstrated an increased in total tau concentration in Alzheimer patients when compared to nondemented aged subjects and with age the concentration of total tau increases systematically [19].

Hyperphosphorylated tau protein

The first methods that demonstrates the hyperphosphorylated tau protein concentration in cerebrospinal fluid were published around 1999. In AD nearly 30 phosphorylation epitopes have been identified [13]. Hyperphosphorylated tau protein has been classified into three subtypes namely: P-tau$_{231P}$, p-tau$_{181P}$ and p-tau$_{199P}$. Increased CSF concentration of P-tau have been found in AD patients [20]. In a study that involve around 2000 patients and controls have shown difference between the subtypes in distinguishing between the AD patients from the control subjects and also from different forms of dementia, p-tau$_{231P}$ and p-tau$_{181P}$ show better results than p-tau$_{199P}$ [21].

Parkinson's Disease

Parkinson's disease is an aged-related neurodegenerative disease and is the second most common neurological disorder after AD, which is characterized by the loss and deterioration of the dopaminergic neurons in the nigral striatal pathway and presence of Lewy pathology [22]. The clinical syndrome include bradykinesia accompanied by several other features like hypertonia, tremor at rest, cognitive impairment and dementia [23].

α-synuclein

α-synuclein is a member of synuclein family of protein, which also includes β and γ-synuclein. The non-Aβ component of Alzheimer's disease (NAC) are the unknown proteins present in the structure of α-synuclein which gives it a unique characteristic as compared to other members of the family [24]. Various studies have described that most of the PD cases are periodic and rare familial forms involving mutations of genes [25]. Mutation in the α-synuclein gene have been associated 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 carry α-synuclein genetic mutations [26]. For the diagnosis of the disease progression, monitoring α- synuclein in the blood and cerebrospinal fluid may be useful.

DJ-1

Mutation of DJ-1 has a very less role in the cause of Parkinsonism however altered levels of DJ-1 in plasma may be helpful in distinguishing between PD patients and healthy individuals [27]. Neuroimaging of the dopamine system is the benchmark biomarker for PD [26]. In clinical research biomarkers are used as a tools to provide early biological readouts in trials of new therapeutics. Increased oxidative stress and neuroinflammation are associated with PD. Concentration of 8- OHDG, an oxidative stress marker is found to be higher in the cerebrospinal fluid of patients with the disease as compared to healthy subjects.

Multiple Sclerosis

Multiple Sclerosis is an autoimmune demyelinating disease of the central nervous system wherein oligodendrocytes and neurons are damaged [28]. It is characterised by demyelination, neuroinflammation with impaired motor function and neurodegeneration [24,29]. Biomarkers in MS can play an important role to improve the diagnostic capacity when screening individuals with the risk of the disease by allowing early diagnosis and preventive therapy [30].

CNS neurofilaments and GFAP

CNS neurofilaments are composed of four subunits namely; heavy chain, medium chain, light chain and α- internexin [31]. Recently, studies have demonstrated that the light chain is more predictable and solid marker in MS. The axonal damage in MS is associated with both heavy and light chain. In both RRMS and progressive MS patients, there is increase in neurofilament levels in CSF when compared to the healthy control subjects and ELISA can be used to determine the neurofilament levels [32]. A study detected an increase in neurofilament level in clinically isolated syndrome and at first diagnosis of MS which suggested that neurofilaments may be an early maker for the disease [33]. Glial fibrillary acidic protein (GFAP) is a transitional filament protein in astrocytes. GFAP is released when the astrocytes are damaged and astrogliosis occurs. High GFAP expression and myelin basic protein (MBP) expression in the CSF results in severe disability in MS patients [34]. In MS, increased MBP expression in the CSF was suggested as an initial marker [35].

CD163

CD163 is a haptoglobin-hemoglobin scavenger receptor and is exclusively expressed in monocytes/macrophages [36]. Macrophages when gets activated cleaves CD163 and forms soluble CD163 (sCD163) in the blood and CSF [34]. For activation of macrophages, serum levels of sCD163 may be an important marker [37]. Subsequent studies have identified increased sCD163 expression both in plasma and in the CSF of patients with MS compared to healthy subjects [38].

YKL-40

YKL-40, a secreted glycoprotein which is expressed in various cell types including vascular smooth muscle cells, chondrocytes, macrophages and hepatic stellate cells [34]. Increased levels of YKL-40 have been observed in various inflammatory conditions namely inflammatory bowel disease and rheumatoid arthritis [39]. In Clinically Isolated Syndrome patients that transduce to MS, the levels of YKL-40

were found to be raised in CSF in comparison to the clinically isolated syndrome patients. A long term study that involves 813 patients with CIS, YKL-40 was associated with shorter term to MS conversion and more rapid disability. Activated microglia and astrocytes in the brain and in the CSF CD14 low monocytes expressed the glycoprotein YKL-40 [40].

Huntington's disease

Huntington disease is a progressive neurodegenerative disease involving cerebral cortex and basal ganglia [41]. Huntington's disease involves unwanted choreatic movements, cognitive impairment, mood disorders, and behavioral changes. The mean age at onset is between 30 and 50 years, with a range of 2 to 85 years. 17 - 20 years is the mean duration of the disease [42]. The pathological changes in central nervous system are reflected by the biomarkers obtained from body fluids, since mutant huntingtin is found on all body tissues [43]. The classification of biomarkers which are attained from the body fluids: metabolic markers, endocrine biomarkers, oxidative stress biomarker, and signalling pathway biomarkers.

Metabolic markers

Mutant huntingtin is expressed due to which peripheral changes may be detected. In peripheral blood HD associated differences in the levels of metabolite was identified by Underwood., et al. that shows metabolic changes in a pro-catabolic pattern, also present in pre-symptomatic HD gene carriers [44]. Uric acid, an antioxidant has been investigated as an important biomarker that could slow down the progression of HD [45].

Endocrine biomarkers

Hypothalamic dysfunction serves to be one among the major cause for loss in weight, depression, disturbed sleep cycle in early stages of HD [46]. With the advancement of disease in HD patients increase in urine cortisol levels was also evident. To track disease, identifying the changes in endocrine are of enthusiasm as biomarkers of HD [47].

Oxidative stress biomarkers

In HD patients, mitochondrial dysfunction has been observed and in pre-symptomatic HD gene carriers in pre-symptomatic HD [48]. Mutant huntingtin and its cleavage products are being investigated as potential biomarkers as the immediate cause of neuronal dysfunction and death in HD [49].

Signalling pathways biomarkers

Brain-derived neurotrophic factor (BDNF) is an agent which helps the neurons to survive have been found to be reduced in symptomatic HD patients serum [50]. BDNF, a neurotrophic gene product if augmented can be a possible therapeutic target in HD [51]. In patients with evident HD and also in pre-manifest HD gene carriers, the endocannabinoid system is found to be normal [52].

Conclusion

Identification of biomarkers for all diseases plays an important role in the advancement of drug discovery and also in the treatment of several types of diseases. Biomarkers helps in identifying the risk, seriousness, stage of the disease and better understanding of the normal physiology, they also help in prediction of the disease, diagnosis and designing the treatment for the specific illness. Biomarkers can be used to replace the clinical endpoints only in the case where the normal physiology of the biological process and the pathophysiology of the process in the disease state is thoroughly understood.

Conflict of Interest

Authors declare no conflict of interest.

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