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Role of Biomarker in the Diagnosis of Neurodegenerative Diseases

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Abstract

Objectives: Biomarker or biological makers are a molecule that behaves as indicators of biological states; ideally they should have high sensitivity, specificity, and accuracy in reflecting the total disease burden. Neurodegenerative diseases are a heterogeneous group of disorders characterized by progressive loss of structure and function of the central nervous system or peripheral nervous system.

Conclusion: Neurological biomarkers are present optimum amount in cerebro spinal fluid (CSF), but they are also present in blood at low levels. In this review we discuss the current status of the biomarkers used in the neurological disorders.

Keywords: Biomarkers; Neurodegeneration; Amyloid; Tau

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Introduction

A biomarker is indicator molecules of a biological as well as pathological condition or pharmacological response to a therapeutic intervention. It can be a simple laboratory test or as complex as a pattern of genes or proteins. In real practical point of view, the biomarker would specifically and sensitively reflect a disease condition and could be used for diagnosis as well as for disease monitoring during and following therapy. Biomarkers with molecular approach can be divided into 3 broad categories [1]:

1. Biomarker that tracks disease progression over time and correlate with known clinical measures.
2. That detects the effect of a drug.
3. In clinical trials it behaves as surrogate endpoints.

Characteristics of a biomarker for neurologic disorders

1. Biomarker should be minimally invasive or non-invasive and produces reproducible results.
2. There are thousands of biomarkers of various diseases including neurologic disorders, but not all of them have been validated.
3. Biomarkers in blood can provide early indicators of disease and help in understanding the pathomechanism of disease as well as determine prognosis.
4. Besides bestowing to diagnosis, biomarkers help in the integration of diagnosis with therapy and are useful for monitoring the course of disease as well as response to treatment.
5. Some biomarkers are potential targets for discovering new drugs for neurologic disorders and are useful for clinical trials during drug development.

Historical background

Bence Jones protein in urine was one of the first biomarkers used in the mid-19th century. During the early 1960s the term "Biomarkers," or biochemical biomarkers started showing their presence in the literature in connection with metabolites and biochemical abnormalities associated with several diseases. During the last decade of the 20th century, the discovery of biomarkers was accelerated by mass spectrometry used for the analysis of biological samples for biomarkers, applications of proteomics for molecular diagnostics, and disclosure of metabolomics for the study of biomarkers. In the blood the best known protein biomarkers are troponin (for myocardial infarction), carcinoembryonic antigen (CEA) for different types of cancer, aminotransferases such as ALT and AST (for liver diseases) and the prostate-specific antigen (PSA) for prostate cancer [2]. In the year 2000 completion of the sequencing of the human genome opened the way for discovery of gene biomarkers. Since 2005, biomarkers play a major role in the field of biotechnology and biopharmaceutical industries. Now a day the term "molecular biomarkers" is commonly used for any molecular modification of a cell on DNA, RNA, and metabolite or protein level.

Of the thousands of biomarkers that have been discovered, most remain to be validated. A biomarker is valid if:

1. It can be measured in a test system with well-established performance characteristics.

2. Evidence for its clinical significance has been established.

Neurodegenerative diseases are mainly identified by progressive loss of cognitive function, dementia, and problems with movements. It leads to the loss of structure or function of neurons, which might also, causes the death of neurons [3-7]. Neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS); Multiple Sclerosis (MS); Huntington's disease (HD); MachadoJoseph disease; Amyloid Polyneuropathy. With extended life expectancy worldwide, neurological disorder increases in the coming years. Nowadays, patients are treated based on symptoms, and currently, no effective known drugs are available to reverse or stop the progression of the diseases. For early and predictive diagnosis of neurodegenerative diseases, enormous efforts are underway [8-10]. Beta-amyloid (Aβ), total tau and its phosphorylated forms (p-tau) are the first biochemical biomarkers of neurodegenerative diseases measured in cerebrospinal fluid (CSF), but, these markers are dependent upon invasive lumbar puncture and therefore it's a cumbersome process for patients [11-13], so there is an urgent need for new biomarkers in more easily accessible body fluids such as peripheral blood. Cortisol is the one of potential biomarkers for neurodegenerative disease and is also used for stress evaluation.

Cortisol

Cortisol is a steroid hormone that is mainly produced by the adrenal glands (cortex region) and by a complex network of the neuroendocrine cascade (coordinated from the brain via a signaling system) known as the hypothalamic pituitary adrenal (HPA) axis. The HPA axis is a key player by which the brain can exert control over physiological activity, which it does in normal activity and also in response to stress. Cortisol crosses the blood-brain barrier easily; owing to its lipophilic character [14]. Binding of cortisol receptors which are present in most the bodily cell to specific intracellular receptors which affect multiple and diverse systems, ranging from regulation of the metabolic, immune, cardiovascular and cognitive systems [15]. This important function makes cortisol a crucial hormone to protect overall health and well-being. When these receptors are activated bind to "hormone response elements" in the DNA and regulate the transcription of target genes [16]. Cortisol also increases blood pressure, and blood sugar levels, and has an immunosuppressive action. Hydrocortisone (synthetic Cortisol) as an antagonist used in the treatment of allergies and inflammation as well as substitute supplementation in cortisol production deficiencies. Cortisol is metabolized by the 11-beta hydroxysteroid dehydrogenase system (11-beta HSD). Any alteration in 11-beta HSD1 has been suggested to play a pivotal role in the pathogenesis of obesity, hypertension, and insulin resistance which ultimately led to osteoporosis, digestive problems, hormone imbalances, cancer, heart diseases and diabetes. Apart from Cortisol, changes in the levels and activities of neurotrophic factors have been observed, such as brain-derived neurotrophic factor (BDNF).

Brain-Derived Neurotrophic Factor (BDNF)

BDNF is a secretory protein, dimeric growth factor presents in most human tissues, including neurons which help to support their survival and encourage neuro- and synaptogenesis and which help to build new brain cells and it keeps your existing brain cells strong [17]. BDNF belongs to the member of the neurotrophin family (growth factors) along with nerve growth factor (NGF); neurotrophins-3 (NT- 3), NT4/5 and NT-6. It is synthesized in the endoplasmic reticulum (ER) as a 32-35 kDa precursor protein (pro-BDNF) that then moves to the Golgi apparatus and trans-Golgi network (TGN). pro-BDNF is sorted by vesicles and subsequently transported into activity-dependent secretion by post-synaptic dendrites. The terminal domain of pro- BDNF is cleaved by a distinct protein convertase enzyme to form 13 kDa biologically active mature BDNF (mBDNF) [18,19]. BDNF is involved in the function and survival of cholinergic neurons in the basal forebrain [20,21]. Whole blood, serum, or plasma have reported significantly lower BDNF levels in patients with major depression [22,23], schizophrenia [24], bipolar disorders [25], autism spectrum disorders or mild cognitive impairment (MCI) [26,27]. It has been described in several other neurodegenerative disorders, including Huntington's disease, Alzheimer's disease and Parkinson's disease. BDNF is stored in platelets, so its concentration in blood derived products, such as plasma and serum, may not be an accurate reflection due to platelet activation and degranulation. Moreover, all previous reports of BDNF levels in CSF in neurodegeneration have used conventional enzyme-linked immunosorbent assays (ELISAs) and have found concentrations below the linear range of the assay, raising doubt as to the validity and accuracy of the reported disease differences [28,29]. The normal range of mean plasma BDNF values was ~92.5 pg/ml (8.0-927.0 pg/ml). It was higher in women and decreased with advancing age in both genders [30]. Stress is a direct response to thoughts we have about the world around us. It is a physical reaction to the issues that confront us. Whilst our brain continues to perceive these situations as threats, stimulating an onslaught of biochemical reactions inside us, we can halt it.

N-acetylaspartate (NAA)

N-acetylaspartate (NAA) level is a neuronal marker or biomarker of functional integrity and vitality in neurons, thus its concentration correlates with neuronal density and neuronal function [31-33]. The nervous system-specific metabolite N-acetylaspartate (NAA), which is synthesized from aspartate and acetyl-coenzyme A in neurons, appears to be a key link in these distinct biochemical features of CNS metabolism. NAA has two primary roles, as a facilitator of energy metabolism in neuronal mitochondria [33], and a source of acetate for fatty acid and steroid synthesis necessary for axonal myelination by oligodendrocytes [34,35]. NAA moves from neurons to the cytoplasm of oligodendrocytes, where apartoacylase (ASPA) cleaves the acetate moiety for the synthesis of fatty acid and steroid and this fatty acids and steroid acts as building blocks for myelin lipid synthesis. Mutations in the gene for ASPA result in the fatal leukodystrophy Canavan disease, for which there is currently no effective treatment. N-acetylaspartate (NAA) is an amino acid derivative, formed by the acetylation of l-aspartic acid, present in very high concentrations (up to 10mM) in mammalian brain and localized predominantly in neurons. It has role in the Neuronal osmolyte that is involved in fluid balance in the brain. Source of acetate for lipid and myelin synthesis in oligodendrocytes, the glial cells those myelinate neuronal axons. Daily turnover of NAA is regulated through an intercompartmental cycle involving extracellular fluids among neurons, oligodendrocytes, and astrocytes [36]. Evidence suggests a continuous NAA efflux from neurons to blood circulation, and in physiological conditions, low serum NAA level relates to its rapid glomerular filtration in the kidneys [37,38]. A slightly decreased NAA level in the brain is a normal part of aging, particularly in older men [39,40]. In contrast, pathological decreases have been observed in the brain of patients with Alzheimer's disease, Parkinson's disease, and multiple sclerosis (MS) by in vivo proton (1H)-magnetic resonance spectroscopy or by postmortem histopathological evidence [41,42]. Low NAA level was found in cortical brain regions of patients with ALS [43-46].

Serum Amyloid P-Component (SAP)

Serum Amyloid P-Component (SAP) is a (PTX2) is a member of the pentraxin family 25kDa homopentameric discoid arrangement of five non-covalently bound subunits glycoprotein first identified as the pentagonal constituent of in vivo pathological deposits called "amyloid" similar to C-reactive protein (PTX1), it is secreted by the liver and a found in plasma at a concentration of approximately 30 mg/L [47]. SAP is a highly conserved an acute phase protein molecule and it is a precursor of amyloid component P which is found in basement membrane and associated with amyloid deposits that may play an important role in innate immunity modulates immunologic responses, inhibits elastase, in human SAP and CRP share 66% homology and the gene for SAP is located on chromosome number 1. One of the unique properties of SAP that it binds both to amyloid plaques and to tau tangles, stabilizing and protecting them against the body's normal clearance mechanism for abnormal protein deposits. The structure of SAP (and CRP) pentamers is a flat disk with a hole in the middle [48,49], containing two Ca^{++} atoms bound to it, and the pentamer thus has 10 Ca^{++} atoms on one side of the disk. Ca^{++} helps in the binding of a variety of molecules including apoptotic debris, bacterial polysaccharides, amyloid deposits, and bacterial toxins [50,51]. Phagocytic cells such as monocytes and macrophages then bind the SAP, CRP and engulf the debris or other material the pentraxin has bound [52]. Further very interesting results provides a research of amyloid precursor protein (APP).

Beta Amyloid

Beta Amyloid is a peptide of 36-43 amino acids produced through the proteolytic processing of a transmembrane protein, amyloid precursor protein (APP), by β- and γ-secretases. In normal physiological condition, more than 90% of Aβ is in the form of $A\beta_{40}$ which is soluble while less than 5% is generated as the longer form of $A\beta_{42}$ which is insoluble; it appears to be the main constituent of amyloid plaques in the brains of Alzheimer's disease patients. The most important isoforms are Aβ-40 and Aβ-42; the smaller form is produced by cleavage that takes place in the endoplasmic reticulum, while the longer form is produced by cleavage in the trans-Golgi network. Aβ-42 is the more fibrillogenic and therefore associated with disease states and thought to be especially toxic. Aβ aggregation is considered to be the primary reason for the neurotoxicity in the classic view, and Aβ oligomers are the most neurotoxic form [53].

Beta-amyloid is a small piece of a larger protein called "amyloid precursor protein" (APP) primarily present in central nervous system, but it is also expressed in peripheral tissues such as in circulating cells is a type 1 membrane glycoprotein that plays an important role in biological activities, including neuronal development, signaling, intracellular transport, and other aspects of neuronal homeostasis. APP consists of a single membrane-spanning domain, a large extracellular glycosylated N-terminus and a shorter cytoplasmic C-terminus. It is one of three members of a larger gene family in humans. In the Alzheimer's brain, abnormal levels of this naturally occurring protein clump together to form plaques that collect between neurons and disrupt cell function. The isoforms of APP can be detected in platelets membrane. The intact 150 kDa weight APP is divided into two forms after platelet activation [54]. The ratio of forms with molecular weight 120–130 kDa and of 110 kDa weight are called "platelet APP isoform ratio," and in AD and mild cognitive impairment (MCI) its ratio decreases not in other dementias [55-60]. The next candidate biomarker is galanine.

Galanin

Galanin is a 29- or 30-amino acid neuroendocrine peptide, isolated in 1983 by Tatemoto K, et al. (1983) [60]. It is found in both the central and peripheral nervous systems and exhibits a variety of physiological effects, acting mainly as an inhibitory, hyper-polarizing neuromodulator, Merchenthaler I, et al. (1993) [61]. The amino acid sequence of galanin is very conserved (almost 90% among species), indicating the importance of the molecule, it has its N-terminal glycine and its C-terminal alanine. The N-terminal end of galanin is crucial for its biological activity and the first 15 amino acids are conserved in all species (the tuna fish being the exception; [59]). The C-terminus is believed to primarily serve as a protector against proteolytic attacks [60,61]. Galanin plays an important biological role in the body, such as regulation of food intake, metabolism and reproduction, regulation of neurotransmitter and hormone release, nociception, intestinal contraction and secretion, and in nervous system its response to injury. This wide diversity of action is mediated by several galanin receptor subtypes. GALR1, GALR2, and GALR3; they are widely expressed in gastric and intestinal smooth muscle cells, in the pancreas, and in the CNS [62]. In the CNS, galanin release several neurotransmitters. In particular, the ability of galanin to inhibit acetylcholine release together with the observation of hyperinervation of galanin fibers in the human basal forebrain of Alzheimer's disease patients suggests a possible role for galanin in this neurodegenerative disorder. Galanin is predominantly an inhibitory, hyperpolarizing neuropeptide and as such inhibits neurotransmitter release. The galanin receptor is often co-localized with classical neurotransmitters such as acetylcholine, dopamine, serotonin and norepinephrine and also with other neuromodulators such as Neuropeptide Y, Substance P and Vasoactive Intestinal Peptide. Besides proteins, microRNAs (miRNAs) have also demonstrated their potential as non-invasive biomarkers from blood and serum for a wide variety of human pathologies [63]. In many disease states altered expression of miRNA, including neurodegeneration, and increasing relevance of miRNAs in biofluids in different pathologies has prompted the study of their possible application as neurodegenerative diseases biomarkers in order to identify new therapeutic targets.

Circulating miRNAs as biomarkers of nervous system diseases

During evolutionary process miRNAs remain conserved, and their expression may be constitutive or spatially and temporally regulated. Increasing efforts to identify the specific targets of miRNAs lead to speculate that miRNAs can regulate more than of human genes. Specific miRNA subsets were expressed in specific brain area and in neuronal and glial cell subtypes [64]. miRNAs play important roles in the transcriptional networks of the human brain, so it's not surprising that changes in brain-specific miRNA expression would be indicative of many pathologies, depression and epilepsy among them. Recently, several groups have proposed the use of microRNAs (miRNAs) circulating in plasma or serum for ND detection [65,66]. miRNAs are small molecules (~22 nucleotides) that play important roles in gene regulation by binding to complementary regions of messenger transcripts and repressing their translation or regulating their degradation [67,68]. On the basis of sequence complementarity analysis, an individual miRNA can bind to and regulate > 100 messenger RNAs (mRNAs), and an mRNA can be regulated by multiple miRNAs; thus, as potential biomarkers, miRNAs are reflective of multiple cellular processes. Over 2000 miRNAs have been discovered in human cells to date, and many of these miRNAs are specific to or overexpressed in certain organs, tissues, and cells [69-86]. Some miRNAs, including

those that are cell-specific, can be enriched in particular cellular compartments, such as neurites and synapses [87-93]. miRNAs can be secreted or excreted into the extracellular space [94-97] and are detectable in plasma and serum [98].

Circulating miRNAs demonstrate stability in the serum and plasma and can cross the blood-brain barrier, thus holding great promise as non-invasive and quantitative biomarkers. To realize the full potential of miRNA biomarkers for nervous system diseases, tools are required for the routine analysis of miRNAs from a range of clinical samples [99].

In the coming years, the need of blood based new biomarker to support the diagnosis of different brain disorders and to help detect progression and response to therapies.

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Conflict of Interest Declaration

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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