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Review Article

Biomarkers of Neurodegenerative Diseases: A Review

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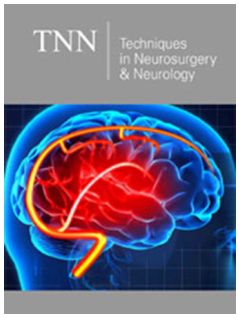

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Abstract

Neurodegenerative diseases create a significant risk to people's health. These age-related disorders are growing increasingly widespread as the elderly population has grown in recent years. Neurodegenerative diseases include Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia, and the spinocerebellar ataxias etc. The causes of these diseases vary, with some impacting memory and cognition and others harming a person's ability to move, speak, and breathe. Effective medicines are essential, but only if the underlying causes and processes of each illness are completely understood. This study gives an outline of biomarkers in neurodegenerative illnesses, comprising the 'core' AD biomarkers amyloid (A) and tau, as well as various disease-specific and generic indicators of neuroaxonal destruction. There are important neurodegenerative pathological biomarkers (amyloid, tau, and -synuclein), a disease intensity biomarker (NfL), synaptic function (neurogranin), and a number of modern analytical platforms (Simoa and MSp).

Keywords: Neurodegeneration; Biomarkers; Alzheimer's disease; Amyloid β; Phosphorylated tau; Neurofilament light; α-Synuclein; Neurogranin

Abbreviations: Aβ: Amyloid β; AD: Alzheimer's Disease; BACE1: β-site APP-Cleaving Enzyme 1; CJD: Creutzfeldt-Jakob Disease; CSF: Cerebrospinal Fluid; ELISA: Enzyme-Linked Immunosorbent Assay; GAP-43: Growth-Associated Protein-43; HAD: HIV-Associated Dementia; HD: Huntington's Disease; IWG-2: International Working Group 2; MCI: Mild Cognitive Impairment; MRI: Magnetic Resonance Imaging; MS: Multiple Sclerosis; MSA: Multisystem Atrophy; MSp: Mass Spectrometry; NFL: Neurofilament Light; Ng: Neurogranin; P-Tau: Phosphorylated Tau; PD: Parkinson's Disease; PET: Positron Emission Tomography; PSP: Progressive Supranuclear Palsy; RT-QuiC: Real-Time Quaking-Induced Conversion Assay; Simoa: Single Molecule Array; SMA: Spinal Muscular Atrophy; SNAP-25: Synaptosomal-Associated Protein-25; SYT-1: Synaptotagmin-1; TDP-43: TAR DNA-Binding Protein 43; TREM2: Triggering Receptor Expressed on Myeloid Cells 2; T-tau: Total Tau; YKL-40: Chitinase-3-like Protein 1

Introduction

The term is made up of the prefix "neuro" which refers to neurons, and "degeneration," which indicates to the loss of structure or function of tissues or organs. As a result, neurodegeneration refers to any disease that predominantly affects neurons. In practice, neurodegenerative illnesses are a broad category of neurological disorders with a wide range of clinical and pathological manifestations that impact subsets of neurons in distinct functional anatomic systems; they develop for unexplained causes and proceed rapidly [1]. Neurodegenerative diseases refer to a group of illnesses caused by the gradual deterioration of neurons and nervous system connections that are necessary for movement, coordination, strength, sensibility, and cognition. Lots of individuals throughout the world suffer from neurodegenerative illnesses. Alzheimer's disease and other memory disorders, ataxia, Huntington's disease, Parkinson's disease, motor neuron disease, multiple system atrophy, and progressive supranuclear palsy are all examples of neurodegenerative illnesses [2]. Biomarkers are the gold standard for diagnosing illness. This is a necessary component of the therapeutic and diagnostic criteria. In neurodegenerative illnesses, such quantitative and conveniently available methods are desperately needed [3].

Biomarkers in Neurodegeneration

Amyloid and tau

The finding of Amyloid (A) and Phosphorylated tau (p-tau) as major components of extracellular plaques and neurofibrillary tangles in Alzheimer's Disease (AD) led to the development of core biomarkers for the disease, with a CSF profile due to a deficiency A42 levels and elevated levels of total tau (t-tau) and phosphorylated tau (p-tau [4]. The decrease in CSF A42 levels is most likely due to preferential retention of A42 in A plaques, whereas the rise in CSF t-tau and p-tau levels is likely due to enhanced tau secretion and phosphorylation from AD-affected neurons [4,5].

Blood Aβ: Novel methods including mass spectrometry and ultrasensitive immunoassays have been used in studies to produce sensitive blood-based A tests [6-10]. Plasma A42, as measured by single molecule array (Simoa) technology, was found to be lower in AD patients compared to controls, and the ratio of plasma A42/A40 was reduced in amyloid PET positive cases in a similar way to CSF, but most studies found more overlap between A-positive and A-negative patients [11,12]. In contrast to Simoa, two recent articles using MagQu's Immunomagnetic Reduction (IMR) technology have shown a rise in plasma A42 in Alzheimer's patients compared to controls, with a negative correlation with CSF A42 [13,14]. Significant heterogeneity across studies persists, with various possible confounders, such as inter-assay variations and putative peripheral an expression, leading to poor concordance and demanding more validation studies to demonstrate the relevance of plasma an in-AD diagnosis [15].

CSFAβ: The most well validated biomarkers in neurodegeneration are CSF A42 [16,17]. In post-mortem investigations, low CSF levels are closely linked to cortical amyloid plaque burden in the neocortex and hippocampus, as well as cortical A deposition evaluated by PET [18,19]. In comparison to A42 alone, the CSF A42/A40 peptide ratio has recently been found to enhance prediction of cortical amyloid deposition and discrimination between Alzheimer's disease and other dementias. This is likely due to normalizing inter-individual variability in A and release into CSF [20,21]. Various studies looked into the significance of alternatively cleaved A peptides in addition to A42. A43, for example, has diagnostic performance equivalent to CSF A42 [22]. The shorter A38 peptide is another A peptide, with evidence indicating a link between CSF A38 levels and amyloid PET [16,23].

CSF tau: T-tau and p-tau concentrations in the CSF are consistently higher in AD [16]. Tau pathology is more strongly linked to cognitive decline than amyloid pathology, with very high CSF t-tau and p-tau levels linked to poorer clinical outcomes [21,22]. While t-tau and p-tau levels broadly indicate disease severity, they have no correlation with the severity of tau pathology as evaluated by PET or in a post-mortem examination [23,24]. The fact that tau proteins may exist in various fragments and have varied phosphorylation patterns has been the focus of recent study, with the expectation that some of them might be disease-specific and represent the underlying pathophysiological processes. In one study, the N-terminal tau fragment truncated at 224 amino acids (N-224) localized with neurofibrillary tangles in brain extracts and showed significantly higher levels in CSF from patients with Alzheimer's disease compared to controls, with higher baseline levels predicting steeper cognitive decline [25]. Tau N-368 has recently been discovered to be considerably higher in the CSF of Alzheimer's patients, with a tau N-368 to total tau ratio demonstrating a strong negative connection with tau PET [26]. Hyper phosphorylation of several CSF tau sites was seen in contrast to healthy controls, indicating that AD pathology has a considerable impact on phosphorylation patterns. Furthermore, in AD CSF, a unique phosphorylation site (T153) has been discovered, which is lacking in non-AD CSF [27]. Many neurodegenerative diseases, including primary tauopathies like Frontotemporal Dementia (FTD) and Progressive Supranuclear Palsy (PSP), do not show elevated tau levels, including specific phosphorylated epitopes (P-tau181, P-tau231, and P-tau199) and N-terminal tau fragments truncated at 224 [25-30]. The increased t-tau and p-tau levels seen in AD could be due to active production and secretion from neurons in response to pathology, rather than a direct reflection of a neurodegenerative process, according to a recent study by Sato et al. [31] using the Stable Isotope Labelling Method (SILK) to investigate tau metabolism [31].

Blood tau: Plasma t-tau levels were also shown to be higher in AD, albeit this was not linked to CSF [32-34]. In recent research by Palmqvist et al. [35], promising findings were found for plasma p-tau, which was quantified utilizing a sensitive immunoassay with electrochemical luminescence detection and showed substantial relationship with tau PET as well as high concordance with CSF p-tau. Several substantial replication studies with strong correlations between CSF p-tau and amyloid PET data were presented at the Alzheimer's Association International Conference 2019 (AAIC), however they have yet to be published. To summarize, while elevated CSF tau levels are a well-established hallmark of Alzheimer's disease, further research into tau biology, particularly its processing, secretion, and aggregation, is needed to completely comprehend tau's significance as an AD biomarker. Additional study on tau pathology biomarkers in other tauopathies, such as PSP, is also required.

Neurofilament light

NFL (neurofilament light) is a kind of intermediate filament found in the cytoplasm of axons and is involved in axonal homeostasis and synaptic transmission [36]. As seen in amateur boxers and ice hockey players [37,38], NfL concentrations rise dynamically in response to concussion. Because it corresponds with neuroaxonal damage in a wide spectrum of neurological illnesses, NfL has also been employed as a biomarker of disease severity [39]. Because the concentrations of CSF and serum NfL are significantly associated, they will be addressed jointly [40,41].

CSF and blood NfL: The degree of whole-brain shrinkage identified on Magnetic Resonance Imaging (MRI) and cognition are connected to serum NfL concentration, which rises a decade before

symptoms manifest in familial AD [42-44]. High plasma NfL levels separate AD, MCI, and healthy controls in sporadic AD, with larger values in MCI participants linked with faster brain shrinkage [45]. Plasma NfL is also linked to the degree of neurofilament staining and post-mortem Break staging [46]. Longitudinal variations in plasma NfL are positively correlated with changes in other neurodegenerative indicators, such as brain atrophy and cognition [47]. In various types of neurodegenerations, NfL is a valuable biomarker. CSF NfL levels have been found to differ between AD and other kinds of dementia; for example, recent post-mortem research found that FTD patients have much greater CSF NfL levels than AD patients. Idiopathic Parkinson's Disease (PD) and atypical parkinsonism, which are clinically indistinguishable at the time of testing, can be distinguished using serum NfL [48-50]. Plasma NfL levels are closely linked to MRI brain volume and clinical severity in Huntington's Disease (HD) and may be a valuable outcome metric in tracking clinical response to disease-modifying therapy [51]. Other neurodegenerative illnesses with high levels of NfL include Amyotrophic Lateral Sclerosis (ALS), HIV-Associated Dementia (HAD), and Creutzfeldt-Jakob Disease (CJD) [52]. In addition to highly high NfL levels, CJD patients have a multi-fold rise in the concentration of a variety of additional CSF indicators, such as total tau, alpha-synuclein, and neurogranin [53-55]. Multiple Sclerosis (MS), a prevalent neuroinflammatory Central Nervous System (CNS) condition, is a good illustration of how NfL might be used as a biomarker outside of neurodegeneration. NfL levels are much higher in MS patients than in healthy controls, and they are linked to the severity of disease activity revealed on MRI [56,57]. Patients with MS who begin disease-modifying medication or transition from first line to a higher-potency treatment, on the other hand, observe a decrease in NfL levels [58]. The findings suggest that NfL in CSF, serum, and plasma is a sensitive but non-specific marker of disease activity in the CNS and Peripheral Nervous System (PNS), with the added benefit of being able to measure disease activity and severity, as seen in MS and HD, as well as treatment response, as seen in MS and Spinal Muscular Atrophy (SMA) [59,60].

α-Synuclein: α-Synuclein is a cytoplasmic protein that has been linked to synaptic transmission and intracellular trafficking [61]. Misfolding and aggregation of α-synuclein into oligomers and fibrils, along with prion-like seeding throughout the CNS, is thought to be central to the pathogenesis of a number of neurodegenerative disorders, including Parkinson's Disease (PD), Multiple System Atrophy (MSA), and Multiple System Atrophy (MSA) [61,62]. α -synuclein has been found in a variety of bio fluids, including CSF, serum, saliva, and tears [63].

CSF α-synuclein: Total α-synuclein is the well-studied protein in CSF, with a meta-analysis finding that levels in synucleinopathies patients are lower than in healthy controls [64]. However, the results are neither sensitive nor specific enough to allow the biomarker to be used for diagnostic purposes, with significant inter-subject and inter-laboratory variation, which is complicated by the fact that blood contamination of the CSF can significantly increase total α-synuclein concentration [65]. Furthermore, one study found that PD patients with a more aggressive clinical course have a greater baseline α-synuclein concentration, further confusing the interpretation [66]. CSF-synuclein levels were shown to be higher in AD than in PD, with exceedingly high levels observed in CJD [67]. More recently, investigations utilizing real-time quaking-induced conversion assay (RT-QuiC) to measure a degree of protein aggregation reliably differentiated between neuropathological verified cases of PD or LBD and controls, with 92-95 percent sensitivity and 100 percent specificity [68,69]. One research found considerable-synuclein aggregation in two control persons who later developed Parkinson's disease years after the sample was taken [70]. In addition to total CSF-synuclein, levels of CSF oligomeric and phosphorylated-synuclein have been reported to be higher in PD when compared to controls, which needs to be confirmed [71].

Blood α-synuclein: Outside of the CNS, the protein is extensively produced, with red blood cells being a major source of -synuclein in the blood and a possible source of contamination [63,72]. synuclein levels in whole blood, plasma, and serum of Parkinson's disease patients have shown mixed findings, limiting its value as a diagnostic biomarker [71]. Studies evaluating oligomeric or phosphorylated versions of the protein in the serum and red blood cells, comparable to CSF, have demonstrated that they are consistently increased in PD patients compared to controls [71,73]. Due to various possible confounding variables, -synuclein is currently one of the most difficult biomarkers to interpret. To establish it as a therapeutically effective biomarker, more research into aggregation tests, as well as oligomeric and Lewy body-enriched forms of the protein, is required.

Neurogranin

Synaptic dysfunction has been found to occur in the early stages of Alzheimer's disease, prior to the development of overt neuronal death [74]. Neurogranin (Ng), a calmodulin-binding postsynaptic protein, is abundant in memory-processing brain areas including the amygdala and hippocampus, where it plays a critical role in long-term potentiation [75].

CSF neurogranin: Multiple studies have demonstrated that Ng levels are greater in AD and MCI patients compared to controls, and that higher levels are associated with a quicker degree of cognitive impairment, a decrease in cortical glucose metabolism, and hippocampus volume loss [76]. CSF Ng increase appears to be unique to AD and has not been observed in other neurodegenerative illnesses outside CJD [53,77,78]. The ratio of peptide-to-total full-length Ng was greater in patients with AD compared to controls in recent research investigating post-mortem parietal and temporal brain tissues, suggesting enhanced processing of Ng into peptides [79]. As a result, the processes driving the elevated CSF Ng in AD might be comparable to those underlying the disease's increased CSF tau processing and release [31].

Blood neurogranin: Few studies have looked at plasma Ng levels, and none have found a significant difference between AD patients and healthy controls; however, pilot studies have found

that the concentration of Ng in neuron-derived exosomes is lower in AD than in controls, and that this is linked to the progression from MCI to AD [80,81]. Overall, the data suggests that Ng is a promising biomarker for early synaptic impairment in Alzheimer's disease, with predictive efficacy in healthy controls and MCI patients in a surprisingly AD-specific way.

Other Biomarker Candidates

The cytoplasmic buildup of TAR DNA-binding protein 43 (TDP-43) is a hallmark of ALS and FTD [82]. TDP-43 pathology is seen in 20-50% of Alzheimer's disease patients, although the protein is difficult to detect in bodily fluids, and CSF TDP-43 appears to be largely sourced from blood [83]. In one research, CSF TDP-43 was shown to be higher in people with ALS and FTD compared to healthy controls, but there was a lot of overlap between the two groups [84]. In another study, plasma TDP-43 levels were shown to be higher in a subset of FTD and AD patients (46 percent and 22 percent, respectively) when compared to controls [85]. There are currently no fluid-based tests available that are selective for pathogenic versions of the protein.

Inflammation has a role in the etiology of Alzheimer's disease, and proteins implicated in the inflammatory response, such as TREM2 and YKL-40 (also known as chitinase-3-like protein 1), might be employed as possible AD biomarkers. TREM2 is expressed in microglia, and its soluble form is increased in the CSF of individuals with MCI and Alzheimer's disease [86-90]. YKL-40 is expressed in astrocytes, and its presence in CSF is associated with the development of BACE1 (-Site APP-cleaving enzyme 1) is an endoprotease involved in the processing of amyloid precursor protein (APP). BACE1 levels in the CSF have been found to be greater in MCI and AD patients than in healthy controls, especially when the APOE 4 allele is present [90,91]. Plasma BACE1 levels were able to predict future MCI to AD progression in another investigation. MCI to AD [88]. Higher levels have also been linked to the severity of tau disease [89]. BACE1 (-Site APP-cleaving enzyme 1) is an end protease that plays an important role in the processing of amyloid precursor protein (APP). BACE1 levels in the CSF have been shown to be greater in MCI and AD patients than in healthy controls, particularly when the APOE 4 allele is present [90,91]. Plasma BACE1 levels were used in another investigation to predict future MCI progression in AD patients [92]. Other synaptic proteins, such as synaptotagmin-1 (SYT-1), synaptosomal-associated protein-25 (SNAP-25), and growth-associated protein-43 (GAP-43), have been found in the CSF of Alzheimer's disease patients and are a promising group of biomarkers, highlighting the importance of synaptic dysregulation in the disease [93-96].

Future Directions

As we optimistically get closer to a day when disease-modifying medicines are available, accurate biomarkers will be required to improve diagnostic accuracy, enabling for earlier diagnosis, better participant selection, and disease activity and treatment impact monitoring. Improving pre-analytical and analytical standardization, identifying new components of neurodegenerative etiology, and developing less invasive fluid biomarkers for screening and monitoring are all future challenges [3].

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