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Review

Biomarkers in Neurodegenerative Disorders

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ABSTRACT

The understanding of neurodegenerative disorders, traditionally seen as well-defined entities with different clinical phenotypes, has significantly transformed over the past 20 years. Diagnosing neurodegenerative disorders mostly requires functional neuroimaging techniques or invasive tests such as lumbar puncture to assess cerebrospinal fluid (CSF). A novel biological approach, particularly through *in vivo* studies, has shifted focus toward CSF and serum biomarkers as indicators of underlying proteinopathies. However, the complexity and heterogeneity of neurodegenerative processes in the central nervous system (CNS), along with overlapping clinical diagnoses, pose significant challenges. Neuroinflammation, a protective response of the CNS, is associated with the pathogenesis of neurodegenerative disorders. The CNS consists of neurons and glial cells, which include microglia, oligodendrocytes, and astrocytes. Various studies have shown the role of neuroinflammatory markers in the formation, diagnosis, and treatment of neurodegenerative diseases. These markers also trigger the formation of various other factors responsible for causing multiple neuronal diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). In this review, we explained the evolving understanding of neurodegenerative disorders, highlighting the importance of CSF and serum biomarkers in diagnosing proteinopathies, as well as the critical role of neuroinflammatory markers in the pathogenesis, diagnosis, and potential therapeutic approaches for various neurodegenerative conditions such as AD, PD, HD, and ALS.

Keywords: Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, neurodegenerative disorders, neuroinflammation, Parkinson's disease.

The sensory system is affected by a large and diverse group of illnesses called neurodegenerative infections. Pathophysiologically, they are represented by a specific cell subpopulation in the brain's contribution and the ensuing clinical manifestation of the condition. The overproduction of precursor proteins, often linked to the formation of abnormal proteins with unstable structures, is a key factor in the development of neurodegenerative disorders. Typically, these altered proteins accumulate as intracellular and extracellular aggregates in affected regions of the brain, potentially contributing to neuronal death.[1] These sums have been identified as biomarkers.

The identification of biomarkers is currently a significant problem in neurodegenerative disorders. According to their definition, biomarkers are objectively quantifiable and assessable indications that successfully differentiate between common organic substances.[1-3]

The present understanding of neurodegenerative disorders, clinical symptoms, neurophysiology, biochemical markers in cerebrospinal fluid (CSF), serum, or specific tissues, neuroimaging techniques, and numerous categories of potential biomarkers from the field of genetics are used. Gene expression detection techniques are becoming more popular in addition to traditional gene analysis. More and more research is also being done in other fields of science, such as proteomics and metabolomics, which analyze functional molecules (proteins and neurotransmitter metabolites) that may have a role in neurodegenerative processes. The main focus is developing a characteristic profile or a collection of

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biomarkers unique to a given clinical unit or a class of disorders with related traits.[2]

In recent years, significant efforts have been made to identify the neuropathological, biochemical, and genetic biomarkers of disorders to diagnose diseases earlier. Biomarkers are biological components that can detect the presence or start of a specific illness.[3] Although autopsy after patient death is currently the gold standard for neuropathological diagnosis. Therefore, the biomarkers for Alzheimer's disease (AD), as well as other neurodegenerative conditions like Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD), must be trustworthy and specific.[4] They also need to help us make more precise diagnoses and provide better care for the conditions.

Neurodegenerative disorders represent one of the leading causes of public health concerns to date, affecting almost 179 million people worldwide. Alzheimer's disease and PD are the first and the second most common neurodegenerative diseases, respectively, both of them being amyloidopathies in which an amyloid protein misfolds and aggregates, causing neurotoxicity and cell death. In the case of AD, the amyloids involved are Tau and Aβ1-42, while in PD, α-synuclein (αSyn) is the one whose misfolding and aggregation leads to toxic inclusions and neuronal death. Throughout the preceding century, researchers endeavored to elucidate the primary pathways and pathological features underlying the initiation and progression of AD and PD. However, many hypotheses have been proposed that amyloid inclusions still represent the only histopathological feature characterizing these diseases. In particular, these entities are Lewy bodies (LB) in PD, intracellular neurofibrillary tangles, and extracellular amyloid plaques in AD. These histopathological hallmarks strictly correlate with the amyloid hypothesis, representing the most studied and controversial ones. The association of this hypothesis with the aforementioned histopathological features underscores its prominence as one of the primary hypotheses of neurodegeneration.[2-5]

ALZHEIMER'S DISEASE

Nowadays, AD diagnosis is based on a clinical evaluation and imaging investigation based on techniques such as positron emission tomography (PET). In contrast, a definitive diagnosis is confirmed only upon a post-mortem examination of the patient's brain. The diagnosis requires detecting dopaminergic neuron loss and the presence of LB and Lewy neurites for PD. Neurofibrillary tangles and amyloid plaques are instead needed to validate the diagnosis of AD. The diagnostic criteria and methods for other neurodegenerative disorders are even less reliable. Computer tomography and magnetic resonance imaging (MRI) scans of patient's brain are employed to provide information about the shape, position, or volume of the tissue, thus offering an overview of the progress of central nervous system (CNS) tissue deterioration when the disease is at an advanced stage. Several molecular imaging compounds have been studied, and four have been approved for clinical use. In particular, florbetaben, florbetapir, and flutemetamol have been approved for the detection of beta-amyloid plaques in the brain, and flortaucipir F18 for the detection of Tau neurofibrillary tangles. Even though amyloid plaques in the brain are a characteristic feature of AD, their detection through PET imaging cannot be used to diagnose the disease. Indeed, Tau neurofibrillary tangles correlate better with cognitive symptoms in AD than amyloid plaques.[4-7]

Moreover, these latter aggregates are not easily detectable with Aβ PET tracers. In addition, Aβ aggregates cannot be considered as a specific hallmark of AD, as amyloid plaques are frequently also found in dementia with Lewy bodies (i.e., the second most common degenerative dementia), as well as in blood vessels in cerebral amyloid angiopathy. Therefore, patients with these conditions show high signals on amyloid PET scans that are similar in pattern to those seen in AD.[6]

Today's older population suffers from dementia, most frequently from AD. In the United States, AD affects more than four million people. It is a chronic, progressive illness that causes neurons and synapses in the brain's cerebral cortex and hippocampus to die. As a result, cognitive abilities like memory, language, judgment and reasoning, and motor coordination deteriorate. The neurotransmitter acetylcholine is used by most of the disease's degenerating neurons to connect with healthy ones.[5]

For the most part, scientists can link the uncommon early-onset familial AD to specific genetic mutations, such as APP gene mutations and presenilin gene mutations, or the late-onset sporadic type to apolipoprotein E.[4-6]

PARKINSON'S DISEASE

Parkinson's disease is a neurodegenerative condition that affects a person a little over 1% of all

adults over the age of 55. It shows up pathologically as a neural nerve degeneration link, specifically between dopaminergic neurons in the striatum and the substantia nigra (SN). According to studies, patients with PD lose the vast majority of the substantia nigra's dopamine-producing cells.[7] The clinical symptoms of PD, such as slowing down of movement, stiffness, and tremors, manifest when these neurons are damaged.

The development of Lewy bodies, which are cytoplasmic inclusions, is another significant neuropathological indicator of PD. The primary protein in it is αSyn.[8] The dopaminergic neurons of SN and others include Lewy bodies. The presence of the αSyn protein discovered inside the Lewy body lesions, which are indicative of PD, and the incident of the dopamine transporter detected by PET imaging are two significant biochemical markers that have been highly effective in identifying the onset of the disease.[9]

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis is an age-related engine neuron neurodegenerative sickness portrayed by the death of upper nerve cells; what's more, lower engine neurons, skeletal muscle decay, loss of motion, and demise.[10] The essential objective of researchers to show straightforwardly comparable to biomarkers of ALS proof of engine neuronal degeneration is the mind or spinal line. To diagnose ALS, track the disease's progression during therapeutic trials, and create potential novel treatments for the condition, biological and substitute markers are being examined.[11]

The primary mechanisms or reasons underlying ALS are currently unknown, although several biochemical alterations brought on by the disease process have been acknowledged.[12]

Upper and lower motor neurons degenerate due to the increased biochemical changes that occur in the motor system in ALS, which in turn causes the clinical symptoms and signs of the disease.[13]

Identifying biomarkers in CSF in ALS is essential for establishing the diagnosis. In the case of ALS, tau protein and p-tau protein could also be useful biomarkers in the differential diagnosis of diseases that manifest similar symptoms. Given that concentration does not correlate with the stage or form of the disease, there is the potential to use them in case of diagnostic doubts at any stage or clinical manifestations.[14]

By simultaneously utilizing multiple markers, we can enhance the diagnostic specificity. While the tau protein demonstrates high sensitivity but low specificity, its integration with p-tau protein can improve diagnostic capabilities. Additional studies and analyses should also be conducted when combining these markers to determine their diagnostic value. It is crucial to consider that the diagnosis of ALS is intricate, necessitating the integration of clinical, electrophysiological, and laboratory data.[14]

HUNTINGTON'S DISEASE

A hereditary disorder called HD is marked by choreiform movements, mental symptoms, and deteriorating dementia over time. Uncontrollable movements in adults typically characterize HD, though stiffness can sometimes be a sign.[15] The autosomal dominant complete penetrance inheritance pattern for the illness. Huntingtin, an abnormal protein, has been discovered in the brain, and the HD gene (IT15) has been located on chromosome 4.[16]

Biomarkers for disorders similar to biomarkers of other neurodegenerative disorders would improve reliable assessment of the efficacy of new treatments and boost the safety and efficiency of clinical trials.[17] Biomarkers will be needed at each stage of the disease, and various detection modalities will be required because the pathophysiology of HD is not yet fully understood.[18] Biomarkers are available to detect changes in energy metabolism and oxidative damage but need to be validated. Imaging technologies have significant promise in the identification of biomarkers.[19]

Recent findings suggest that artificial intelligence (AI) methods predict cognitive patterns in normal subjects, indicating pre-dementia stages. For example, Chudzik et al.[20] used granular computing rules to classify cognitive data from the BIOCARD study, which has been ongoing for over 20 years with 354 normal subjects. The study's findings suggest that AI methods can predict patterns in cognitive attributes of everyday subjects that might indicate their pre-dementia stage, which may not be visible to neuropsychologists.

Another study based on BIOCARD data provides a significant advancement in detecting and predicting AD, utilizing AI methods to identify early cognitive changes. Over 20 years, subjects were evaluated annually to determine their cognitive status-normal, mild cognitive impairment, or dementia. The study used the Clinical Dementia Rating Sum of Boxes as

a quantitative index for assessing mild dementia and developed a rough set of rules for classification. Researchers discovered that some subjects showed signs of potential cognitive impairment or mild dementia that were not evident to neuropsychologists. These findings highlight the capacity of AI methods to detect subtle cognitive changes that might indicate a pre-dementia stage.[21]

This approach is a critical step forward in the early detection of AD. By identifying patterns in cognitive attributes among normal subjects, AI methods can reveal early signs of dementia, offering a window for intervention before the condition becomes clinically apparent. Many neurodegenerative disorders have limited treatment options due to the lack of early diagnostic technologies, preventing therapeutic drugs from being administered to damaged neurons before they die. However, significant progress has been made in identifying biomarkers for these diseases. Epigenetics, which studies heritable changes in gene expression without alterations in the deoxyribonucleic acid (DNA) sequence, links the genome to its environment. Accumulated epigenetic changes over time may contribute to neurodegeneration.[22]

One intriguing area in contemporary neuroscience is the role of epigenetic mechanisms in maintaining homeostasis and function in the CNS and their regulation in disorders. Abnormal gene expression changes in neurodegeneration are thought to be influenced by epigenetic controls such as DNA methylation and histone modification. Molecular diagnostics are valuable tools for detecting and diagnosing neurological illnesses, including Alzheimer's and Parkinson's. Early diagnosis enables timely medical intervention and participation in significant clinical trials.[23]

Recently, many epigenetics-based treatments have been developed for various neurodegenerative illnesses. Typical epigenetic and transcriptional alterations have been identified as biomarkers of early-stage neurodegenerative disorders. The potential for innovation and practical application of these biomarkers is substantial, significantly enhancing their reliability. Epigenetic biomarkers are valuable in clinical practice for diagnosing, monitoring, and forecasting diseases in patients with neurodegenerative conditions.[24]

In conclusion, the journey toward effective early detection and intervention for neurodegenerative disorders hinges on researchers' collaborative efforts to advance our understanding of genetic and biochemical biomarkers. Identifying these markers in diverse populations can unravel the complexities of disease mechanisms, leading to groundbreaking insights into pathogenesis. Biochemical markers, in particular, hold promise for refining diagnostic precision and tailoring therapeutic strategies. However, considering their specificity to disease stages and types, the nuanced application of biomarkers necessitates a multi-faceted approach. Combining various biomarkers can significantly enhance diagnostic accuracy, specificity, and sensitivity. It is imperative to acknowledge that biomarkers should complement, not replace, thorough clinical evaluations to yield holistic insights. Comprehensive clinical trials are indispensable for validating superior biomarkers, illuminating the pathophysiology of neurodegenerative disorders, and optimizing patient outcomes. The urgent need for cost-effective, accessible diagnostic tools for early disease detection cannot be overstated, particularly given the limitations of current imaging techniques like PET and MRI. These methods, while valuable, are often prohibitively expensive, pose health risks with repeated use, and sometimes need to differentiate between neurodegenerative conditions accurately. Post-mortem analyses, though definitive, come too late for meaningful intervention. Therefore, the quest for reliable, non-invasive biomarkers continues, with the ultimate goal of transforming early diagnosis and treatment paradigms for neurodegenerative disorders.

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