Advances in Bioresearch
Adv. Biores., Vol 15 (1) January 2024:162-167

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.15.2.162167

Advances in Bioresearch

REVIEW ARTICLE

Emerging Biomarkers in Neurological Disorders: Promises and Challenges in Diagnosis

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ABSTRACT
Neurological illnesses can be difficult to diagnose and are frequently discovered at an advanced stage, which can affect patient outcomes and treatment effectiveness. The field of biomarker research has shown great promise in transforming the ways that diseases like Parkinson's, Multiple Sclerosis, and Alzheimer's are diagnosed. This paper provides a thorough analysis of the field of developing biomarkers in neurological illnesses, including future prospects, accompanying obstacles, and prospective uses. Genetic biomarkers play a crucial role in risk assessment and focused therapies by revealing disease vulnerability and underlying processes. Imaging biomarkers, which include MRI, PET, and fMRI, provide unique insights into anatomical and functional changes, facilitating early diagnosis and disease surveillance. Biochemical markers that are isolated from blood or CSF offer vital surrogates for pathology unique to a particular disease, improving diagnostic precision and tracking the course of the illness. But there are several obstacles to overcome, including issues with standardisation, validation, and the morality of using biomarkers. Ethical frameworks, standardised procedures, and strong validation studies are essential for successful clinical translation. Longitudinal studies, AI, and collaborative initiatives utilising multi-omics techniques provide interesting avenues for biomarker research in the future. This review combines the most recent research, illuminating the potential and challenges of novel biomarkers in the diagnosis of neurological disorders and opening the door to more individualised treatments and improved patient care.
Keywords*: Biomarkers, Neurological Disorders, Diagnosis, Challenges, Future Directions.*

Received 24.10.2023 Revised 06.12.2023 Accepted 16.03.2024

How to cite this article:
Harisinh P, Iype C, Dany J, Aniket A, Abhijit P. Emerging Biomarkers in Neurological Disorders: Promises and Challenges in Diagnosis. Adv. Biores., Vol 15 (2) March 2024: 162-167

INTRODUCTION

Neurological illnesses comprise a broad range of ailments that impact the neurological system and provide significant hurdles to diagnosis as well as significant global health consequences. Because of their intricacy, these illnesses frequently result in incorrect or delayed diagnosis, which impedes prompt therapies and worsens patient outcomes. Finding trustworthy biomarkers has become a game-changing strategy that offers neurological illness early detection, precise prognosis, and focused therapies.

The field of diagnosis has changed in recent years due to research on biomarkers, especially in common neurodegenerative diseases including Multiple Sclerosis (MS), Parkinson's disease (PD), and Alzheimer's disease (AD). The role of genetic markers in determining the likelihood and course of disease has attracted significant attention. Critical genetic variants associated with neurological illnesses have been found using genome-wide association studies (GWAS), which can help with risk assessment and provide insights into the processes underlying disease [1]. Notably, the identification of mutations in genes such as LRRK2 in Parkinson's disease and APOE4 in Alzheimer's disease has fundamentally changed our knowledge of disease susceptibility and possible treatment options [2].

The ability to see both structural and functional changes in neurological illnesses has been made possible by significant advancements in neuroimaging methods. Functional MRI (fMRI), PET/PET, and magnetic resonance imaging (MRI) have all contributed to our understanding of the connectivity changes, brain morphology, and neurochemistry related to these illnesses [3]. For example, imaging biomarkers,

including tau and amyloid buildup in AD or dopaminergic system malfunction in PD, have made it possible to diagnose and track the disease's course early [4]. Nonetheless, there are still issues with standardising imaging procedures and interpreting various imaging results from various centres [5].

In addition to genetic and imaging indicators, biochemical markers have become essential instruments for deciphering the complex pathophysiology of neurological disorders. Biomarkers such as amyloid-beta, tau, alpha-synuclein, and neurofilament light chain proteins that are extracted from either blood or cerebrospinal fluid (CSF) act as stand-ins for pathological processes unique to a certain illness [6]. Interestingly, these indicators help with monitoring disease development and treatment response in addition to diagnostic efforts [7]. Their clinical value is, however, hampered by problems with assay standardisation, sampling procedure variability, and dynamic biomarker profiles [8].

These biomarkers hold great potential, but a number of obstacles prevent them from being easily incorporated into clinical practice. Standardisation and validation continue to be significant obstacles [9]. The creation of broadly recognised biomarkers is hampered by inconsistent outcomes, inconsistent study designs, and inconsistent methodology. To determine the validity and potential therapeutic use of these indicators, comprehensive validation studies with sizable and varied cohorts are essential [10].

The application of biomarkers in neurological illnesses is heavily influenced by ethical issues. A careful approach is required to address concerns about patient privacy, consent, fair access, and potential stigma associated with predictive biomarkers [11]. In addition, it is essential to exercise caution while navigating regulatory frameworks and ethical norms when implementing research findings in clinical settings to guarantee patient-centric and morally acceptable procedures [12].

There are opportunities as well as difficulties in the rapidly changing field of biomarker research in neurological illnesses. To surmount obstacles and fully use these biomarkers for better patient outcomes, strong cooperative efforts between researchers, physicians, regulatory agencies, and patients are necessary. By outlining prospective uses and addressing the many obstacles preventing the clinical translation of new biomarkers in neurological illnesses, this review seeks to provide a thorough examination of the present status of this field.

Section 1: Neurological Disorders and Genetic Biomarkers

Numerous clinical symptoms and complex aetiologies define neurological illnesses, which frequently include underlying genetic predispositions that affect disease susceptibility and development. Deciphering the complex genetic landscape of neurological diseases has made genetic biomarkers essential building blocks.

Deciphering the genetic architecture of different neurological diseases has been made possible in large part by genome-wide association studies (GWAS). Numerous genetic variations linked to higher illness risk, changed protein function, or disturbed pathways implicated in neurological disorders have been found by these investigations [1]. For example, the APOE gene polymorphism, especially the ε4 allele, is one of the strongest genetic risk factors for Alzheimer's disease. AD patients who carry the APOE ε4 allele have an increased risk of the illness and frequently show symptoms earlier in life [2]. Similar to this, mutations in genes such as LRRK2, PARKIN, and SNCA have been associated with familial forms of Parkinson's disease, providing insight into important biochemical processes involved in the degradation of dopaminergic neurons [3].

Comprehending these genetic markers facilitates risk assessment and reveals possible targets for treatment. Approaches to precision medicine that are customised to a person's genetic profile show promise for improving therapeutic treatments and treatment plans. For example, genetic testing has made it easier to identify certain mutations in some epilepsy subtypes, which has guided the choice of more potent antiepileptic drugs and provided prognostic information [4].

Moreover, genetic indicators provide light on disease processes by revealing the complex biochemical cascades and pathways involved in neurological illnesses. For example, mutations in genes encoding proteins involved in RNA processing, such SOD1 or C9orf72, in Amyotrophic Lateral Sclerosis (ALS) provide insight into abnormal RNA metabolism and protein aggregation as important factors in the pathophysiology of the illness [5]. Similar to this, Huntington's disease is caused by the HTT gene's expansion of CAG repeats, which results in the synthesis of mutant huntingtin protein and sets off a series of processes that eventually lead to neuronal degeneration [6].

The field of genetic biomarker research has progressed from studying monogenic correlations to polygenic risk scores, which use a combination of genetic variations to determine a person's total risk of developing certain neurological illnesses. Gene predisposition may be understood comprehensively by polygenic risk scores, which are obtained from many genetic loci throughout the genome. These ratings support population-wide risk assessment and lead to a more thorough knowledge of disease susceptibility [7].

Despite the fact that genetic biomarkers provide significant insights, there are still issues with their clinical translation. The accurate prediction of illness start and progression purely based on genetic markers is complicated by variability in penetrance, phenotypic heterogeneity, and gene-environment interactions [8]. In addition, cautious ethical frameworks and patient-centered methods are required due to ethical concerns surrounding genetic testing, which include concerns about privacy, informed permission, and potential psychological effects [9].

To sum up, genetic biomarkers are extremely useful tools for understanding the genetic basis of neurological conditions. They facilitate risk classification, provide critical insights into disease causes, and have the potential to direct individualised treatment approaches. However, tackling issues with accuracy, interpretation, and ethical implications is necessary for a thorough incorporation into therapeutic practice.

Section 2: Progress and Uses of Imaging Biomarkers

Modern imaging methods have transformed our knowledge of neurological illnesses by providing previously unattainable insights into the anatomical, functional, and molecular changes that occur in the brain. Functional MRI (fMRI), Positron Emission Tomography (PET), and Magnetic Resonance Imaging (MRI) are essential diagnostic and research techniques for neurological illnesses. They help find imaging biomarkers.

A non-invasive imaging method called magnetic resonance imaging (MRI) offers precise structural pictures of the brain that make it possible to see anatomical alterations linked to a range of neurological disorders. Hippocampal atrophy and cortical thinning are indicators of the illness's development in Alzheimer's disease that are made easier to identify by MRI, which helps in early identification [1]. Additionally, in diseases like Multiple Sclerosis, MRI's capacity to identify white matter lesions and evaluate cerebrovascular alterations is critical for determining disease activity and directing therapy choices [2].

In neurodegenerative illnesses, PET imaging—which uses radiotracers to visualise molecular processes—has proven crucial. In vivo evaluation of protein aggregation is made possible by the use of PET ligands that target the tau and amyloid-beta proteins in Alzheimer's disease, which helps with early diagnosis and disease progression tracking [3]. Similar to this, employing radiotracers like [18F]FDOPA or [11C]DTBZ for PET imaging of the integrity of the dopaminergic system in Parkinson's disease provides information about the severity of the illness and aids in evaluating the efficacy of treatment [4].

An effective method for measuring brain activity and connection changes linked to neurological illnesses is functional magnetic resonance imaging, or fMRI. Understanding the pathophysiology of diseases like epilepsy and schizophrenia has been aided by the discovery of disturbed functional connectivity networks in these illnesses by means of resting-state fMRI, which measures spontaneous oscillations in the brain [5]. Furthermore, task-based fMRI has clarified modified brain activation patterns, which helps map cognitive deficiencies in neurodegenerative disorders or assist with presurgical planning in epilepsy [6].

Notwithstanding these developments, there are still obstacles in the way of imaging biomarkers' broad clinical acceptance. Inter-study variability is limited by data analysis methodologies, scanner platform variability, and standardisation of imaging processes [7]. Moreover, obstacles to the normal application of modern imaging techniques in clinical settings include financial concerns, accessibility to specialised imaging facilities, and the requirement for specialised knowledge [8].

Furthermore, the dynamic character of changes in neurological illnesses and confounding variables must be carefully taken into account when interpreting imaging biomarkers. For an accurate diagnosis and prognosis, extensive multimodal imaging methods are necessary due to heterogeneity in illness presentation and overlapping imaging findings between various disorders [9].

To sum up, biomarkers for imaging are essential for revealing the structural, functional, and molecular changes that underlie neurological illnesses. Cutting-edge imaging methods provide priceless insights into the pathophysiology of diseases, supporting early diagnosis, tracking the course of the illness, and directing treatment approaches. Successful integration of these imaging biomarkers into normal clinical practice requires addressing issues with standardisation, accessibility, and interpretation.

Section 3: Biochemical Markers: Deciphering the Pathophysiology of Disease

Biochemical indicators obtained from peripheral blood or cerebrospinal fluid (CSF) have shown to be extremely useful in deciphering the complex pathophysiology of neurological illnesses. These markers, which include proteins, metabolites, and other compounds, act as stand-ins for pathological processes unique to a certain illness, providing information on the underlying mechanisms of the disease and aiding in efforts related to diagnosis and prognosis.

The pathogenesis of Alzheimer's disease (AD) may be greatly understood by analysing CSF biomarkers, such as tau and amyloid-beta (Aβ) proteins. Increased levels of tau pathology and total and phosphorylated tau in CSF are indicative of neuronal degeneration and can help distinguish Alzheimer's disease (AD) from other dementias by indicating the severity of the disease [1]. Furthermore, the identification of modified Aβ42 levels, exhibiting reduced concentrations in Alzheimer's disease patients, functions as a marker of amyloid plaque accumulation, facilitating prompt diagnosis and disease tracking [2].

As with AD, CSF biomarkers are important indicators of underlying inflammatory and neurodegenerative processes in Multiple Sclerosis (MS). Neurofilament light chain (NfL) protein levels in CSF are one example of a marker that serves as an indication of treatment response and disease progression since it correlates with neuronal damage and disease activity [3]. Furthermore, myelin-specific proteins, such as CSF oligoclonal bands or myelin basic protein (MBP), help in the diagnosis and tracking of MS [4].

Blood-based biomarkers have attracted interest due to its potential in non-invasive monitoring and diagnosis, in addition to CSF biomarkers. Although difficult to use because of blood-brain barrier restrictions, blood-based biomarkers in neurological illnesses have the benefit of being easily accessible and sampled. For example, neurofilament light chain (NfL) plasma levels have become a potential blood biomarker for neuroaxonal damage in illnesses such as multiple sclerosis (MS) and several neurodegenerative disorders [5].

Blood metabolic signatures and other molecular markers may be useful in identifying changes unique to a certain illness. Blood sample metabolomic analysis makes it possible to identify distinct metabolic fingerprints connected to neurological conditions. Unique alterations in metabolites associated with oxidative stress, energy metabolism, or neurotransmitter pathways provide information on the processes underlying illness and possible targets for treatment [6].

Nevertheless, there are also issues with using biochemical indicators in neurological illnesses clinically. Careful interpretation and validation across a range of populations is required due to the standardisation of test methodologies, individual heterogeneity in biomarker levels, and dynamic changes in biomarker profiles during the course of illness evolution [7]. Furthermore, comorbidities and drug adverse effects might complicate the interpretation of biomarker levels, necessitating cautious thought in clinical interpretation [8].

In summary, biochemical markers obtained from blood and CSF offer important new understandings of the pathogenic mechanisms behind neurological illnesses. These indicators support early diagnosis, track the evolution of the illness, and evaluate the efficacy of treatment. To fully utilise biochemical markers for better clinical treatment of neurological illnesses, it is imperative to overcome standardisation, validation, and interpretation problems.

Section 4: Difficulties with Validation and Standardisation of Biomarkers

Although biomarkers hold great promise for transforming neurological illness diagnosis and treatment, a number of obstacles impede their effective transition from experimental settings to clinical settings. Validation, standardisation, and repeatability of biomarkers are the most pressing difficulties.

Before biomarkers may be incorporated into standard clinical practice, it is imperative that their clinical value be validated. Extensive and heterogeneous patient populations require rigorous validation studies in order to determine the predictive usefulness, sensitivity, specificity, and accuracy of biomarkers [11]. It is important to replicate results across various populations and stages of illness in order to verify the dependability and applicability of biomarker performance.

Still a major obstacle to overcome is coming to an agreement on standard operating procedures for biomarker testing and data interpretation. Discrepancies in biomarker values are caused in part by variability in assay methodology, which include sample collection, storage, processing methods, and analytical platforms [12]. Ensuring consistent and comparable outcomes across various laboratories and clinical contexts requires harmonising these approaches.

Furthermore, addressing the intrinsic complexity and variability within neurological illnesses is necessary for the validation of biomarkers. Comprehensive validation procedures suited to individual disease settings are required due to the wide range of clinical presentations, illness subtypes, and varying disease progression trajectories [13]. When assessing the efficacy of biomarkers and their significance for clinical decision-making, stratification according to illness stage, subtype, or severity may be essential.

In biomarker research, reproducibility across several trials and contexts is another crucial factor that is frequently contested. Inter-study heterogeneity presents challenges to the reliable replication of biomarker findings due to variations in patient populations, methodology, and data analysis procedures [14]. Enhancing repeatability and facilitating cross-validation of biomarkers requires standardised reporting rules and cooperative efforts to exchange data and methodology.

Moreover, regulatory and ethical frameworks must be carefully taken into account when translating biomarkers into clinical practice. The ethical and appropriate use of biomarkers in clinical practice depends on adherence to legal requirements as well as ethical considerations pertaining to patient permission, privacy, and data sharing [15]. Ethical concerns encompass matters of fairness regarding biomarker-based diagnostics accessibility, guaranteeing that progress serves all patient groups.

Multidisciplinary stakeholders, including researchers, doctors, regulatory bodies, and industry partners, must work together to address these issues. The establishment of consortia or networks devoted to biomarker validation, standardisation, and data sharing can be facilitated by cooperative efforts to create best practices and consensus norms [16]. Furthermore, encouraging open-access platforms and archives for the exchange of biomarker data and techniques might help to increase study repeatability and transparency.

In conclusion, despite the enormous promise of biomarkers in neurological illnesses, a number of critical obstacles pertaining to validation, standardisation, and repeatability must be overcome before they can be successfully incorporated into clinical practice. To fully use biomarkers for improved patient care and outcomes, strong validation studies, standardised assay techniques, extensive data sharing, and adherence to ethical rules are essential.

Section 5: Future Directions and Ethical Considerations

The application of biomarkers in neurological illnesses raises a number of ethical issues that demand thoughtful analysis and preemptive action to guarantee ethical and just practices. Concurrently, it is essential to foresee future paths that capitalise on technical developments and cooperative endeavours in order to enhance biomarker research while maintaining ethical standards.

Moral Aspects to Take into Account

When it comes to ethical issues in biomarker research, privacy concerns are paramount. Concerns about patient privacy, confidentiality, and data security are brought up by the gathering and processing of sensitive biological data, such as genetic or neuroimaging data [17]. Protecting patient autonomy and confidentiality requires strict adherence to privacy legislation, informed consent procedures, and strong data protection measures.

Ensuring that all patient groups benefit from developments in neurological disease diagnoses requires equitable access to biomarker-based diagnostics. It is necessary to work towards reducing socioeconomic obstacles and promoting inclusion in order to address discrepancies in access to healthcare resources, such as specialised diagnostic tools or biomarker-based testing [18]. Initiatives that collaborate with legislators, medical professionals, and advocacy organisations are crucial to advancing fair access to biomarker-driven diagnostics.

Furthermore, the prognostic properties of some biomarkers raise moral questions about the psychological effects on those who receive this knowledge. Concerns regarding psychological discomfort, stigma, or prejudice may arise from predictive biomarkers, such as those that indicate a person's propensity to develop neurodegenerative disorders [19]. Ensuring informed consent on the implications of biomarker testing, together with providing proper counselling and support services, are therefore critical ethical issues.

Prospective Courses

Prospective future avenues in biomarker research for neurological illnesses are made possible by cooperative efforts and technical developments. Comprehensive insights into the intricate interactions between biological processes underlying neurological illnesses can be gained by multi-omics techniques that integrate genomes, proteomics, metabolomics, and other -omics disciplines [20]. By combining multi-omics data, new treatment targets and biomarkers can be found.

Machine learning and artificial intelligence (AI) have enormous promise for sifting through large information and finding patterns that may be invisible to the human eye. Through the analysis of complex data sets from imaging, genomics, and biochemical tests, AI systems can support personalised therapy, biomarker identification, and predictive modelling [5]. But it's important to address ethical questions about the transparency and biases built into AI programmes.

Furthermore, prognostication, therapy response, and disease progression can all be greatly aided by longitudinal studies that monitor biomarker profiles over time. In order to enable tailored therapies and improve patient care, longitudinal biomarker studies can clarify the dynamic changes in biomarker profiles and their relationship with disease trajectory [6].

Responsible biomarker research must be guided by ethical frameworks and norms that proactively address developing technologies and possible ethical consequences. The development of ethical standards that strike a balance between innovation and ethical principles depends critically on

stakeholder interaction, which includes patients, advocacy organisations, researchers, and policymakers [7].

CONCLUSION

In conclusion, striking a careful balance between scientific advancement and ethical concerns is necessary to navigate the ethical terrain when determining the course of future biomarker research for neurological illnesses. Using biomarkers to their greatest potential for better diagnosis and tailored therapies requires respecting the values of patient autonomy, data privacy, equity, and openness.

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