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RESEARCH INVENTION JOURNAL OF SCIENTIFIC AND EXPERIMENTAL SCIENCES 2(1):1-5, 2023

©RIJSES Publications ISSN: 1597-2917

Novel Biomarkers for Early Detection of Neurodegenerative Diseases using Liquid Biopsy

Okafor, Azubuike Ikechukwu and Emuru, Edward Odey

Department of Medical Biochemistry, University of Cross River State, Calabar, Nigeria
Email: okafor.azubuike@gmail.com; phone number: +2348035723454

ABSTRACT

Neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic lateral sclerosis (ALS), represent a significant global health challenge, exacerbated by the aging population. Early detection is critical to improving patient outcomes, but current diagnostic methods are invasive, costly, and not conducive to large-scale screening. Liquid biopsy, a minimally invasive technique analyzing biofluids like blood, presents a promising alternative for early detection through novel biomarkers. This paper explores the potential of liquid biopsy for identifying early-stage biomarkers in neurodegenerative diseases, discussing the emerging biomarkers, the challenges in their validation, and the future direction of this technology in clinical applications.

Keywords: Neurodegenerative Diseases, Liquid Biopsy, Early Detection, Biomarkers, Alzheimer's Disease.

INTRODUCTION

More than 55 million people worldwide are currently living with dementia, with nearly 60% of them having a diagnosis of Alzheimer's disease (AD), the most common and well-studied cause of neurodegeneration. AD is a highly heterogeneous disease characterized by a mixture of genetic, biochemical, cellular, and vascular changes in the brain. In most affected individuals, these processes begin decades before the emergence of overt cognitive symptoms suggestive of dementia, when brain degeneration is already advanced. Therefore, early detection of AD has become a major goal of research efforts considering the severe social and economic burden posed by this condition. Current diagnosis typically relies on clinical assessment consisting of neuropsychological tests in combination with neuroimaging and/or biochemical screening for cerebrospinal fluid (CSF) biomarkers. These strategies are not amenable to screening large populations due to their high cost, invasiveness, and the lack of accessibility to specialized facilities and trained personnel [1, 2, 3]. In this context, several candidate blood-based biomarkers related to AD pathology have emerged during the last decade. This development is accompanied by the introduction of simple and widely available procedures for blood sampling, storage, and transportation. As a result, blood-based biomarkers for AD are likely to have great public health relevance due to their potential for global distribution. Liquid biopsy is a non-invasive sampling method of biofluids to obtain biomarkers that reflect underlying pathological changes at specific tissues or organs to be analyzed. In the central nervous system (CNS), biofluids such as CSF, serum, and plasma are being assessed to detect pathological modifications in neurodegenerative diseases, particularly blood. As a biofluid, blood is advantageous because of its simple and less invasive collection and transportation procedures, as well as its relatively low cost and global accessibility, making it suitable for large-scale screening protocols [4, 5, 6].

NEURODEGENERATIVE DISEASES: OVERVIEW AND CURRENT DIAGNOSTIC CHALLENGES

Neurodegenerative diseases are a broad category of disorders caused by the degeneration of the nervous system. They impact millions of patients worldwide, and the projections related to neurodegenerative diseases suggest that these numbers will be even higher in the upcoming years. Therefore, the importance of early disease detection to increase the quality of life for these patients cannot be understated. Neurodegenerative diseases portray a variety of phenotypes, including a widespread memory loss and an

overall cognitive decline. Patients may also exhibit uncontrolled movements, hyperactivity, personality changes, and seizures, along with other symptoms that vary based on the population of neurons affected [7, 8, 9]. Neurodegenerative diseases such as Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), Vascular dementia, Pick's disease, and many others constitute one of the most important public health challenges today, especially with the increase in the elderly population. For example, as of 2020, there were over 80 million people aged over 65 in Europe alone. Alzheimer's disease is the most common neurodegenerative disease, constituting 62–70% of all dementias, with over 40 million patients worldwide, and considered 94.6 billion USD in costs in the United States alone. Current diagnosis of neurodegenerative diseases occurs when the disease is already advanced. However, diagnosing these diseases early on is essential. Indeed, it has been shown that the sooner disease-modifying medications are administered, the more effective they are [10, 11, 12].

LIQUID BIOPSY: PRINCIPLES AND APPLICATIONS

Historically, various sampling methods such as blood, cerebrospinal fluid (CSF), and even saliva have been employed to locate sources for clinical diagnostic purposes. However, the focus has now shifted to the term "liquid biopsy." A liquid biopsy can be defined as a minimally invasive analysis of biofluids (often blood) in search of novel biomarkers. These markers are typically of a cellular or acellular nature, including, but not limited to, circulating tumor cells (CTCs), exosomes/vesicles, cell-free DNA, or RNA. Since its emergence in 2003, the field of liquid biopsy has exploded, eventually paving the way for diverse applications. The most extensively studied malignancies in this context have been the high morbidity cancers, namely, breast, colorectal, prostate, and lung cancer. However, the successful implementation of liquid biopsies in oncology paved the way for more research within fields, including heart diseases, autoimmune diseases, and, more recently, the ever-looming neurodegenerative diseases [13, 14, 15]. The scientific basis of liquid biopsy relies on the existence of biofluid components containing vital information that reflect the tissue of origin. During disease initiation and progression, cells from the original environment typically undergo mechanistic changes. As a result, these cells release their cellular and acellular contents into the blood or other body fluids. Biofluid components can be classified as "cell-based" components (e.g., red blood cells, white blood cells, CTCs, and exosomes) or "acellular" components (e.g., circulating free DNA (cfDNA) and circulating RNA (cRNA)). Based on this classification, liquid biopsy approaches can be further categorized into sampling the cellular and acellular components described above. However, components obtained from liquid biopsy alone are often ambiguous and nonspecific for a particular disease since they are generally present in both healthy and diseased states. Therefore, liquid biopsy alone is insufficient to establish a diagnosis. In order to enhance the selectivity of the identified components, liquid biopsy must also be coupled with subsequent characterization [16, 17, 18].

EXISTING BIOMARKERS FOR NEURODEGENERATIVE DISEASES

Currently available neurodegeneration biomarkers primarily serve as research tools for studying physiological mechanisms and disease progression and have limited clinical use. Biomarkers for neurodegenerative diseases fall into three categories, with each containing a subcellular component. The first category, "broad pathogenesis biomarkers," targets general pathophysiological features of neurodegenerative diseases and are predominantly based on proxies of the intracellular accumulation of misfolded proteins that define the various neurodegenerative diseases (tau, phosphorylated tau 181, phosphorylated tau 217, Aβ42, and t-tau). The second category, "specific pathogenesis biomarkers," aims to detect neurodegenerative disease-specific pathophysiological processes (e.g., transactive response DNA binding protein 43 [TDP-43] for frontotemporal dementia [FTD], and α-synuclein for synucleinopathies). Saliva, blood, and urine have emerged as biofluid samples in the search for novel biomarkers for the early detection and monitoring of neurodegenerative diseases (smartphone-based Functional tests, and portable Hand-held visual field analyzer). The third category consists of "cell communication biomarkers" that measure different components released from injured cells into the biofluids. When detected in biofluids such as blood, urine, or saliva unlike CSF, these biomarkers can serve as indicators of the pathophysiological mechanisms occurring in the CNS. Current candidate biomarkers and those under investigation largely come from CSF analysis and/or postmortem brain tissues. CSF analysis offers many advantages over biofluid samples, particularly in terms of signal-to-noise ratio (SNR) and the absence of blood-brain barrier (BBB) issues in the sampling process and the detection of CNS-specific biomarkers. However, acquiring CSF samples requires lumbar puncture, an invasive and unpleasant procedure for patients [19, 20, 21].

EMERGING BIOMARKERS FOR EARLY DETECTION

Emerging novel biomarkers at the beginning stages of translation from bench to bedside show promise in early detection of neurodegenerative diseases using Liquid Biopsy. Neurodegenerative diseases are

broadly characterized by pathological accumulation of proteins that lead to neuroinflammation, neurodegeneration, and loss of cognitive functions. The current gold standard for diagnosis is based on neuropsychological assessments followed by structural imaging techniques such as MRI. Possible interventions including disease-modifying drugs are now in late-stage clinical trials but effectuate now because of the late onset of symptoms as brain onset years before clinical diagnosis. Although neuroimaging techniques like PET can be used to diagnose neurodegenerative diseases by detecting the pathological proteins in-tracerebrally, they are aggressive, expensive, and lack the availability of infrastructures worldwide. Consequently, there is a worldwide demand for the discovery of biomarkers for early diagnosis to facilitate better treatment [22, 23, 24]. Neurodegenerative diseases can be also detected at the pre-symptomatic stage using different biofluids, Fluids in the peripheral circulation can be analyzed, which represent a reflection of physiological and biochemical activities occurring in cells. They are also known to play a critical role in intercellular communication. Therefore, searching for biomarkers in biofluids is of utmost importance, as it would allow easy accessibility and high feasibility for screening. Several blood-based biomarkers including Aβ42/Aβ40 ratio, plasma neurofilament light chain (Nfl), phosphorylated tau181, tau aggregate in exosomes, and more show promise in early detection. With the advancement of high throughput techniques and novel non-invasive technologies, progress is made in the identification of biomarkers using saliva, tears, urine, and cerebrospinal fluids. There is a growing hope that such biomarkers could be conveniently analyzed and allow the identification of patients at the pre-symptomatic stage of the disease [25, 26].

FUTURE DIRECTIONS

Unfortunately, current diagnostic approaches based on invasive brain biopsies, neuroimaging, and CSF analyses, are expensive, time-consuming, and far from ideal. Thus, a sizable clinical need exists for low-cost, non-invasive, sensitive, and technically simple diagnostic assays that allow the early detection of these disorders and can be administered repetitively to follow disease progression and treatment response [22, 24]. Exosomes, microvesicles, apoptotic bodies, and exudation from tissues are just a few of the vesicles shed by cells into various biological fluids that are known as extracellular vesicles (EVs). As a result of their unique lipid membrane, EVs are stable and resistant to cellular degradation and environmental factors, such as pH, temperature, and hypoxia. EVs are present in all bodily fluids and reflect the origin, physiological state, and surrounding environment of their parent cells. Accordingly, EVs emerged as powerful mediators of intercellular communication, and growing interest in their potential as disease biomarkers has been reported during the past decade. Plasmatic EVs are of particular interest as they can be readily obtained from patients, and peripheral collection is relatively convenient compared to obtaining other bodily fluids, such as cerebrospinal fluid [23, 25].

CONCLUSION

The development of novel biomarkers for the early detection of neurodegenerative diseases through liquid biopsy holds immense promise for transforming clinical practice. As research advances, these biomarkers could enable non-invasive, cost-effective, and widely accessible screening methods, facilitating earlier diagnosis and improved management of these debilitating conditions. However, significant challenges remain in the validation and standardization of these biomarkers for clinical use. Future research should focus on refining these techniques and ensuring their robustness and reliability, paving the way for their integration into routine clinical practice and ultimately improving patient outcomes on a global scale.

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CITE AS: Okafor, Azubuike Ikechukwu and Emuru, Edward Odey (2023). Novel Biomarkers for Early Detection of Neurodegenerative Diseases using Liquid Biopsy. RESEARCH INVENTION JOURNAL OF SCIENTIFIC AND EXPERIMENTAL SCIENCES 2(1):1-5.