American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Review Article

For Early Diagnosis of Neurodegenerative Diseases: Acting of Biomarkers

Yanxiang Li, Zhuoyang Zhang, Chenci Xu, Jiawen Gan and Yanhua Yao*

Department of Biochemistry and Molecular Cell Biology, Shanghai Jiao Tong University, China

***Corresponding author:** Yanhua Yao, Department of Biochemistry and Molecular Cell Biology, School of Medicine, Shanghai Jiao Tong University, Shanghai 200025, China.

To Cite This Article: *Yanxiang Li, Zhuoyang Zhang, Chenci Xu, Jiawen Gan, Yanhua Yao. For Early Diagnosis of Neurodegenerative Diseases: Acting of Biomarkers. Am J Biomed Sci & Res. 2020 - 11(3). AJBSR.MS.ID.001628.* DOI: 10.34297/AJBSR.2020.11.001628.

Received: December 14, 2020; **Published:** December 17, 2020

Abstract

Neurodegenerative disease is a kind of progressive and incurable diseases caused by neuron degeneration and leads to cognitive impairment and dyskinesia. The prevalence of neurodegenerative diseases increases with age and the age of neurodegenerative diseases tends to be younger. Biomarkers, discovered from blood or cerebrospinal fluid to imaging, are helpful in diagnosis of neurodegenerative diseases, especially in early and differential diagnosis, which can help choose the proper treatment. This review will focus on biomarkers used in Alzheimer's disease, Parkinson's disease and Prion disease diagnosis and recent advancements in biomarker discovery.

Keywords: Neurodegenerative disease, Biomarkers, Alzheimer's Disease, Parkinson's Disease, Prion Disease

Introduction

With the intensification of global aging, neurodegenerative diseases are spreading day by day, seriously affecting people's physical and mental health and quality of life. Neurodegenerative diseases are commonly including Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), prion disease, etc. [1]. The main pathological changes of these diseases are the loss of neuronal cells or the degeneration of neuronal cell structure and function, but the specific reasons leading to these pathological changes have not been discovered yet. The progressive degeneration of neurons will finally cause problems with ataxias and dementias. Moreover, neurodegenerative diseases are still in the situation of low consultation rate, high misdiagnosis rate and low treatment rate. Therefore, early diagnosis is particularly important for timely intervention and treatment.

At present, the differential diagnosis of most neurodegenerative diseases mainly relies on the examination of clinical signs. For example, for PD diagnosis, when symptoms such as tremor and muscle stiffness appear, it indicates that many dopaminergic neurons in the substantia nigra compact part of the midbrain have been lost. However, clinical physical examination alone is not enough to diagnose neurogenerative diseases, so sensitive, specific, and economical neurogenerative diseases biomarkers are recommended. The related biomarkers of different neurodegenerative diseases that have been reported so far are of great significance to clarify the pathogenesis of the disease and could be used for the early differential diagnosis of the disease and the monitoring of disease progression, as well as the evaluation of current and future treatment methods, and provide a new direction for the treatment and prognosis of the neurodegenerative diseases.

Alzheimer's Disease (AD) Biomarkers

AD is the most common neurodegenerative disease which also represents approximately 60-70% of dementia cases. Its brain pathological features include the accumulation of the protein fragment β-amyloid (plaques) outside neurons in the brain and twisted strands of the protein tau (tangles) inside neurons. Finally, neurons supporting basic somatic function like swallowing and walking will be destroyed and leads to the death. Now a consensus has been established that it is critical to diagnose and treat patients in pre-clinical stage of AD. The diagnosis requires signs or symptoms

of AD and one or more pathological biomarkers [2]. It is currently recognized that ptau181, t-tau and Aβ42 are the core biomarkers of AD [3]. A meta-analysis confirmed that the combination of them can improve accuracy of the diagnosis [4]. In 2018, National Institute of Aging-Alzheimer's Association (NIA-AA) proposes the "A/T/N" framework that divides AD biomarkers into 3 categories based on three brain pathological changes of AD [5]. A includes Aβ42 in the cerebrospinal fluid (CSF) and other biomarkers that can represent β-amyloid [5]. A scientist shows that the level of Aβ42 in CSF of AD patients is approximately 50% of the normal individuals of the same age [6], while growing evidence suggest that β-amyloid (Aβ)42/40 CSF concentration ratio performs better than Aβ42 concentration alone in AD diagnosis [7]. T includes p-tau in CSF. p-tau181 was shown to be able to reflect the degree of neurodegeneration and cognitive decline [8]. The specificity of p-tau will increase with the progression of AD [9]. Tau PET has a high correlation with low metabolism and atrophy of the brain [10]. N represents neurodegeneration. 18F-FDG-PET, reflecting the loss of nerve fibers and synapses, and functional defect of nerve, could be used to predict AD with a sensitivity and specificity of 82% and 100% [11].

Parkinson's Disease (PD) Biomarkers

PD, characterized by rest tremor, muscular rigidity, and bradykinesia, is the second common neurodegenerative disease with 0.3% global incidence which rises to above 3% among people aged 80 and older [12,13]. Early prominent death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and abnormal aggregates of αsynuclein protein, called Lewy bodies and Lewy neurites is the main pathological features of PD [14]. There is no specific cerebrospinal fluid (CSF) or other laboratory tests for PD. However, evidence show that biomarkers in CSF and blood, such as αsynuclein, DJ-1, coenzyme Q10 and glial fibrillary acidic protein (GFAP), are potential in early diagnosis and differential diagnosis of PD [15-17]. But these biomarkers' sensitivity and specificity are still not good enough. Additionally, imaging biomarkers are more promising in the diagnosis of PD. The imaging biomarkers include dopamine transporter single-photon emission computed tomography scans (DAT SPECT), fluorodopa positron emission tomography (F-DOPA PET), transcranial sonography (TCS) and magnetic resonance imaging (MRI) [15]. DAT SPECT can visualize dopamine degeneration in the nigro-striatum [18] and is approved by the US Food and Drug Administration for use when the diagnosis is difficult [19]. TCS is involved in PD diagnosis by an enlarged area of echogenicity in the substantia nigra but is not sensitive enough for early diagnosis of PD [20]. MRI has become a standard technique that is routinely used in patients with PD to exclude secondary causes and in some cases helps diagnosing PD [21].

Prion Disease Biomarkers

Prion disease, also called transmissible spongiform encephalopathies (TSEs), is a degenerative condition that leads to death in both animals and humans, caused by the deposition of many pathogenic prion proteins (PrPsc) formed by conformational changes of cellular prion proteins (PrPc) in cells [22]. The human prion diseases comprise Creutzfeldt-Jakob disease (CJD), variably protease-sensitive prionopathy, Gerstmann-Sträussler-Scheinker disease, fatal familial insomnia, and kuru [23]. CJD is the most common prion disease and Sporadic Cruetzfeldt-Jacob disease accounts for 85% of all CJD cases with annual worldwide incidence of 1-2 cases/million population [24,25]. Several biomarkers of rapid neurodegeneration in prion disease have been discovered, including14-3-3, tau, NSE (Neuron-specific enolase) and S100B. 14-3-3, a conserved soluble acidic protein widely found in various eukaryotic cells, is mediating intercellular signal transduction and a range of physiological functions. Its increased levels in CSF could suggest neuronal damage, prion disease and other neurological disorders [26]. In the CSF of CJD disease patients, the protein tau level is also significantly increased. NSE, one of the enolases involved in glycolytic pathway, shows the highest activity in brain tissue cells. Abnormal NSE is one of the causes of neurodegenerative disease, and NSE can be detected in the CSF of patients with CJD. Additionally, the increased level of a type of astrocyte protein, S100B indicates the increase of astrocyte activity [27]. Moreover, combining of different biomarkers testing results can lead to a more specific and accurate diagnosis. For example, the specificity and sensitivity of protein 14-3-3 and protein tau in CJD patients could be 96% and 84, respectively, meanwhile at a low p-tau (phosphorylated tau)/t-tau (total protein tau) ratio, the specificity and sensitivity of the combined 14-3- 3 test are 96% and 79%, respectively [28,29]. These two methods are currently the most accurate methods to diagnose CJD, but they are still currently in laboratory stage.

Discussion

Neurodegenerative diseases are a common cause of cognitive impairment in older people. Its diagnosis is difficult but finding the key features can help make proper diagnosis. And early diagnosis and treatment can effectively slow down the progression of these diseases. Biomarkers of neurodegenerative diseases are essential for early diagnosis and differential diagnosis. Unique and sensitive biomarkers can not only diagnose diseases effectively, but also track the progression of the diseases to determine if the treatment works. Ideal biomarkers have not been discovered up to now. The known biomarkers are not sensitive enough to help diagnose and can only be the reference. However, through the joint detection and analysis of multiple biomarkers, accuracy can be significantly

improved. Additionally, the mostly used biomarkers such as CSF, brain MRI and PET are invasive and expensive, so their usage are limited. Therefore, more research is needed to find the sensitive, specific, less invasive and cheap biomarkers for diagnosis. More and more researchers focus on blood and other body fluid to find out better biomarkers. Although there are no treatments available for cures of these diseases, treatment trails are underway. With progress of our understanding of the pathology, mechanisms and genetics, a large step forward can be made in preventing or slowing the neurodegenerative diseases progression.

References

1. Peng C, JQ Trojanowski, VM Lee (2020) Protein transmission in neurodegenerative disease. Nat Rev Neurol 16(4): 199-212.
2. Dubois B, Harald Hampel, Howard H Feldman, Philip Scheltens, Paul Aisen, et al. (2016) Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. Alzheimers Dement 12(3): 292-323.
3. Molinuevo JL, Scott Ayton, Richard Batrla, Martin M Bednar, Tobias Bittner, et al. (2018) Current state of Alzheimer's fluid biomarkers. Acta Neuropathol 136(6) :821-853.
4. Ineke A van Rossum, Stephanie Vos, Ron Handels, Pieter Jelle Visser (2010) Biomarkers as predictors for conversion from mild cognitive impairment to Alzheimer-type dementia: implications for trial design. J Alzheimers Dis 20(3): 881-891.
5. Clifford R Jack Jr, David A Bennett, Kaj Blennow, Maria C Carrillo, Billy Dunn, et al. (2018) NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 14(4): 535-562.
6. Blennow K, E Vanmechelen (2003) CSF markers for pathogenic processes in Alzheimer's disease: diagnostic implications and use in clinical neurochemistry. Brain Res Bull 61(3): 235-242.
7. Piotr Lewczuk, Natalia Lelental, Philipp Spitzer, Juan Manuel Maler, Johannes Kornhuber (2015) Amyloid-β 42/40 cerebrospinal fluid concentration ratio in the diagnostics of Alzheimer's disease: validation of two novel assays. J Alzheimers Dis 43(1): 183-191.
8. Harald Hampel, Kaj Blennow, Leslie M Shaw, Yvonne C Hoessler, Henrik Zetterberg, et al. (2010) Total and phosphorylated tau protein as biological markers of Alzheimer's disease. Exp Gerontol 45(1): 30-40.
9. Jack CR, David A Bennett, Kaj Blennow, Maria C Carrillo, Howard H Feldman, et al. (2016) A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology 87(5): 539-547.
10. Scheltens P, Kaj Blennow, Monique M B Breteler, Bart de Strooper, Giovanni B Frisoni, et al. (2016) Alzheimer's disease. Lancet 388(10043): 505-517.
11. Ding Y, Jae Ho Sohn, Michael G Kawczynski, Hari Trivedi, Roy Harnish, et al. (2019) A Deep Learning Model to Predict a Diagnosis of Alzheimer Disease by Using (18)F-FDG PET of the Brain. Radiology 290(2): 456-464.
12. Pringsheim T, Nathalie Jette, Alexandra Frolkis, Thomas D L Steeves (2014) The prevalence of Parkinson's disease: a systematic review and meta-analysis. Mov Disord 29(13): 1583-1590.
13. Poewe W, Klaus Seppi, Caroline M Tanner, Glenda M Halliday, Patrik Brundin, et al. (2017) Parkinson disease. Nature Reviews Disease Primers 3: 17013.
14. Kalia LV, AE Lang (2015) Parkinson's disease. Lancet 386(9996): 896-912.
15. Lotankar S, KS Prabhavalkar, LK Bhatt (2017) Biomarkers for Parkinson's Disease: Recent Advancement. Neurosci Bull 33(5): 585-597.
16. Mischley LK, Leanna J Standish, Noel S Weiss, Jeannie M Padowski, Terrance J Kavanagh, et al. (2016) Glutathione as a Biomarker in Parkinson's Disease: Associations with Aging and Disease Severity. Oxid Med Cell Longev 2016: 9409363.
17. Magdalinou N, AJ Lees, H Zetterberg (2014) Cerebrospinal fluid biomarkers in parkinsonian conditions: an update and future directions. J Neurol Neurosurg Psychiatry 85(10): 1065-1075.
18. Seifert KD, JI Wiener (2013) The impact of DaTscan on the diagnosis and management of movement disorders: A retrospective study. Am J Neurodegener Dis 2(1): 29-34.
19. Armstrong M, MS Okun (2020) Diagnosis and Treatment of Parkinson Disease: A Review. Jama 323(6): 548-560.
20. Bouwmans AE, Annemarie M M Vlaar, Werner H Mess, Alfons Kessels, Wim E J Weber, et al. (2013) Specificity and sensitivity of transcranial sonography of the substantia nigra in the diagnosis of Parkinson's disease: prospective cohort study in 196 patients. BMJ Open 3(4): e002613.
21. Berg D, Jonathan D Steinberger, C Warren Olanow, Thomas P Naidich, Tarek A Yousry, et al. (2011) Milestones in magnetic resonance imaging and transcranial sonography of movement disorders. Mov Disord 26(6): 979-992.
22. Nandi PK, E Leclerc, D Marc (2002) Unusual property of prion protein unfolding in neutral salt solution. Biochemistry 41(36): 11017-11024.
23. Ironside JW, DL Ritchie, MW Head (2017) Prion diseases. Handb Clin Neurol 145: 393-403.
24. Mead S, Michael P H Stumpf, Jerome Whitfield, Jonathan A Beck, Mark Poulter, et al. (2003) Balancing selection at the prion protein gene consistent with prehistoric kurulike epidemics. Science 300(5619): 640-643.
25. Imran M, S Mahmood (2011) An overview of human prion diseases. Virol J 8: 559.
26. Meissner B, K Kallenberg, P Sanchez Juan, D Collie, D M Summers, et al. (2009) MRI lesion profiles in sporadic Creutzfeldt-Jakob disease. Neurology 72(23): 1994-2001.
27. Beaudry P, P Cohen, J P Brandel, N Delasnerie Lauprêtre, S Richard, et al. (1999) 14-3-3 protein, neuron-specific enolase, and S-100 protein in cerebrospinal fluid of patients with Creutzfeldt-Jakob disease. Dement Geriatr Cogn Disord 10(1): 40-46.
28. Zerr I, M Bodemer, S Räcker, S Grosche, S Poser, et al. (1995) Cerebrospinal fluid concentration of neuron-specific enolase in diagnosis of Creutzfeldt-Jakob disease. Lancet 345(8965): 1609-1610.
29. Bahl JM, Niels H H Heegaard, Gerhard Falkenhorst, Henning Laursen, Hans Høgenhaven, et al. (2009) The diagnostic efficiency of biomarkers in sporadic Creutzfeldt-Jakob disease compared to Alzheimer's disease. Neurobiol Aging 30(11): 1834-1841.