Soluble Neuregulin-1 as a Diagnostic Biomarker for Alzheimer’s Disease

Hyunjong Liew1 and Sang Hyung Lee2*

1Department of Bio and Fermentation Convergence, College of Natural Sciences, Kookmin University, 77 Jeongneung-Ro, Seongbuk-Gu, Seoul, South Korea
2Department of Neurosurgery, College of Medicine, Seoul National University, SMG-SNU Boramae Medical Center, Seoul, 156-707, South Korea

Abstract

Diagnosis using a biomarker is a faster and cheaper than brain imaging. Diagnostic biomarkers are chosen based on the characteristics of the disease, specificity, sensitivity, and stability during all disease stages. For this reason, previous candidates with insoluble form in a pathophysiologic stage are not useful as biomarkers for the early stage of a neurodegenerative disease. In this study, we explored the possibility of using soluble proteins in cerebrospinal fluid, blood, or other peripheral materials as diagnostic biomarkers, in particular, the availability of soluble neuregulin-1 in blood.

Keywords: Diagnostic biomarker; Alzheimer’s disease; Peripheral detection of brain disease; Neuregulin-1

Introduction

Several types of dementia have been identified, such as Alzheimer’s dementia, vascular dementia, dementia with Lewy bodies, and frontotemporal dementia. Mild cognitive impairment (MCI) and corticobasal degeneration are also occasionally included in the dementia category. Among them, Alzheimer’s dementia and vascular dementia comprise up to 50% of cases with dementia [1]. It is crucial to distinguish between these two diseases for which the treatment method is slightly different. This study focuses on Alzheimer’s disease (AD).

Diagnostic biomarkers are essential for a quick and easy diagnosis of Alzheimer’s dementia at its early stage. Till date, biomarkers established for Alzheimer’s dementia are associated with the amyloid beta (Aβ) protein, such as Aβ42 itself or the ratios of the Aβ42 and Aβ40 isoforms in the cerebrospinal fluid (CSF) [2], soluble amyloid precursor protein (APP), phospho tau, or apolipoprotein E [3-5]. Many studies have reported that CSF Aβ42 levels in patients with AD are approximately half of those in control [6-11]. Patients with AD have increased soluble APP (sAPP) β and sAPPα levels compared with those in non-demented controls [12]. However, this should not preclude the development of an accurate biomarker. This study aimed to determine the utility of soluble neuregulin-1 (sNGR-1) as a biomarker for AD.

Detection Methods for Neurodegenerative Diseases of the Brain

AD is primarily diagnosed using behavioral testing. The most common tests include general cognitive function screening tools, such as the Mini-Mental State Examination for Dementia Screening (MMSE-DS) and the Information-Memory-Concentration test. The reliability of these tests has been confirmed in a correlational study on senile plaque and neurofibrillary tangle intensity [13]. However, it can be difficult to distinguish a person of low intelligence from a patient with dementia using cognitive function tests. If the test result indicates dementia, magnetic resonance imaging (MRI) must be used to confirm the diagnosis, which is expensive and time consuming. Therefore, a simple, quick method is needed before proceeding with a more expensive test, even if the diagnosis is less accurate.

AD accounts for 50% of dementia cases. Voxel-based morphometry (VBM) is often used to confirm Alzheimer’s dementia [14]. This method focuses on the pathophysiological changes in the hippocampus or the entorhinal cortex, which are vulnerable to the disease and changes in these areas indicate MCI or AD [15].

Some methodologies detect decreased grey matter volume by T1-based three-dimensional (3D) brain structural imaging, voxel-based diffusion tensor imaging analysis [16] or a perfusion analysis using arterial spin-labeled MRI in patients with Alzheimer’s dementia [17].

Mostly, pulse sequence 3D T1-weighted imaging called magnetization prepared rapid acquisition gradient echo or spoiled gradient recalled have been used to diagnose AD [18,19]. A region of interest is used in T1 contrast brain 3D imaging; however, errors in evaluation based on subjective judgment can occur with this method because it is often used to analyze a specific area [20].

T1 brain structural imaging by VBM calibrates electrical signal intensity of white matter and grey matter loss, enabling objective diagnosis using brain region segmentation [21]. However, none of these imaging methods are convenient or fast. Therefore, diagnostic reagents or kits for biomarkers are required.

Choice of peripheral materials

Sampling from the body is inevitably accompanied by pain. Moreover, the brain is not included in the peripheral area. Therefore, blood plasma or CSF is the major tissues to detect diseases originating from the brain. A plasma biomarker is particularly useful because collecting plasma or serum is noninvasive and easier than collecting CSF by lumbar puncture [22].

A change in the state of the brain is not easy to detect because of the insolubility of the majority of disease-related proteins, such as tau, amyloid beta, and alpha-synuclein, which have been proposed as candidate diagnostic biomarkers for AD. However, these molecules tend to accumulate in the diseased brain tissue and may leak into peripheral areas as per the disease progress.

The ideal diagnostic biomarker molecule should be detectable at every disease stage and have a high specificity and sensitivity.

*Corresponding author: Sang Hyung Lee, Department of Neurosurgery, College of Medicine, Seoul National University, SMG-SNU Boramae Medical Center, Seoul, South Korea, 156-707; Tel: +82-2-870-2302; E-mail: nslee@snu.ac.kr

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Neuregulin-1 as a diagnostic biomarker

Membrane-anchored NRG occurs abundantly in the prefrontal cortex, hippocampus, cerebellum and substantia nigra [23-28]. NRGs are expressed by various immune cells, such as astrocytes, oligodendroglial cells, microglial cells, and neurons, in the brain [25,29-31]. NRGs are cleaved by proteases into presenilin-1 or 2, are converted to a free-floating form, and act as soluble factors [32]. sNRG binds to the erbB4 receptor, which provides a synaptogenic feature, or it migrates to an inflamed region [33]. In other cases, NRGs regulate N-methyl-D-aspartate (NMDA) receptor function in pyramidal neurons and are thus related to NMDA receptor dysfunction by decreasing channel activity in patients with schizophrenia [34,35]. NRGs are also associated with neural development, nerve cell differentiation, neuronal migration, neurite outgrowth, synapse formation, axonal myelination, dendritic development and neurotransmitter receptor expression [36].

sNRG-1 can be detected in CSF and brain tissue [37]. Interestingly, sNRG-1 levels increase in the CSF of patients with AD, and the NRG-1 receptor erbB4 is also found in CSF where it functions to repress astrocytic differentiation [38]. In our previous report, we confirmed that endoplasmic reticulum stress-mediated neurotoxicity increases oligomeric Aβ, particularly when treated with NRG-1, which was confirmed by phospho-eIIF-2a activity. NRG-1β is strongly expressed in the hippocampal dentate gyrus of 14 month old Tg2576 mice with tissue deformation in the early stage of AD compared with that inagematched controls. Based on these results, we predicted that sNRG-1 would increases in patients with AD [39]. As a results, plasma sNRG-1 levels in 60 patients with mild and moderate AD were significantly higher than those in 55 healthy controls, and a significant correlation was observed between sNRG-1 levels and MMSE scores [40].

Conclusion

For diagnosis in neurodegenerative brain disease, development of diagnostic biomarker has been a commitment because it makes possible to faster, cheaper and accurate diagnosis than brain imaging or mental and behavior test. In order to be a diagnostic biomarker, it must be detected to be available throughout the stage of the disease, and only a patient of specific disease should be clear quantitative changes. It should be limited only in specific diseases. NRG-1 is generated by the enzyme, presenilin activated by a disease; it amplifies the toxicity of beta amyloid. We suggested a possible diagnosis of the disease by detecting the molecule associated with the pathogenesis in peripheral blood. For the preparation of patient sampling, real difficulty is the finding of early onset patients. Almost of all patients in hospital have already moderate or severe symptoms. In case of study using the disease suspicious group, epidemiological studies should be parallel with biomarker development. Nonetheless, biomarker studies are expected to be very useful for confirmation of the diagnosis and treatment efficiency. Biomarker diagnostic kit will come for fast, easy-handle and inexpensive tool.

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