Journal of
Alzheimer's Disease & Parkinsonism

Liew and Lee, J Alzheimers Dis Parkinsonism 2016, 6:5
DOI: 10.4172/2161-0460.1000271

Mini Review Open Access

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

Hyunjeong Liew[1] and Sang Hyung Lee[2]*

[1]Department of Bio and Fermentation Convergence, College of Natural Sciences, Kookmin University, 77 Jeongneung-Ro, Seongbuk-Gu, Seoul, South Korea
[2]Department 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 pathophysiological 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 (sNRG-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

Received September 01, 2016; **Accepted** October 10, 2016; **Published** October 17, 2016

Citation: Liew H, Lee SH (2016) Soluble Neuregulin-1 as a Diagnostic Biomarker for Alzheimer's Disease. J Alzheimers Dis Parkinsonism 6: 271. doi: 10.4172/2161-0460.1000271

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-eIF-2α 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 in age-matched 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, presenillin 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.

References

1. Molsa PK, Marttila RJ, Rinne UK (1986) Survival and cause of death in Alzheimer's disease and multi-infarct dementia. Acta Neurol Scand 74 : 103-107.
2. Mizoi M (2014) Distinction between mild cognitive impairment and Alzheimer's disease by CSF amyloid beta40 and beta42 and protein-conjugated acrolein. Clin Chim Acta 430: 150-155.
3. Dobrowolska (2014) Diurnal patterns of soluble amyloid precursor protein metabolites in the human central nervous system. PLoS One 9: e89998.
4. Chiu MJ (2014) Plasma tau as a window to the brain-negative associations with brain volume and memory function in mild cognitive impairment and early Alzheimer's disease. Hum Brain Mapp 35:3132-3142.
5. Koffie RM (2012) Apolipoprotein E4 effects in Alzheimer's disease are mediated by synaptotoxic oligomeric amyloid-beta. Brain 135: 2155-2168.
6. Zhao FYD, Yang L (2014) Protein-based biomarkers in cerebrospinal fluid and blood for Alzheimer's disease. J Mol Neurosci 54: 739-747.
7. Lahiri DK (2013) Abnormal cerebrospinal fluid (CSF) dynamics in Alzheimer's disease and normal pressure hydrocephalus: CSF-amyloid beta precursor protein metabolites as possible biomarkers. Eur J Neurol 20: 211-213.
8. Lewczuk P (2012) Cerebrospinal fluid soluble amyloid-beta protein precursor as potential novel biomarkers of Alzheimer's disease. J Alzheimers Dis 28: 119-125.
9. Mandic G (2008) Cerebrospinal fluid amyloid beta and tau protein: Biomarkers for Alzheimer's disease. Vojnosanit Pregl 65: 901-905.
10. Marksteiner J, Hinterhuber H, Humpel C (2007) Cerebrospinal fluid biomarkers for diagnosis of Alzheimer's disease: Beta-amyloid(1-42), tau, phospho-tau-181 and total protein. Drugs Today (Barc) 43: 423-431.
11. Blennow K (2004) Cerebrospinal fluid protein biomarkers for Alzheimer's disease. NeuroRx 1: 213-225.
12. Wu G (2012) Characterization of plasma beta-secretase (BACE1) activity and soluble amyloid precursor proteins as potential biomarkers for Alzheimer's disease. J Neurosci Res 90: 2247-2258.
13. Blessed G, Tomlinson BE, Roth M (1938) The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry 114: 797-811.
14. Kakeda S, Korogi K (2010) The efficacy of a voxel-based morphometry on the analysis of imaging in schizophrenia, temporal lobe epilepsy, and Alzheimer's disease/mild cognitive impairment: A review. Neuroradiology 52: 711-721.
15. Frisoni GB (2010) The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol 6: 67-77.
16. Abe O (2010) Voxel-based analysis of the diffusion tensor. Neuroradiology 52: 699-710.
17. Jahng GH and Schuff N (2009) Influence of selecting EPI readout-encoding bandwidths on arterial spin labeling perfusion MRI. MAGMA 22: 287-295.
18. Brant-Zawadzki M, Gillan GD, Nitz WR (1992) MP RAGE: A three-dimensional, T1-weighted, gradient-echo sequence--initial experience in the brain. Radiology 182: 769-775.
19. Yamashita E (2006) Evaluation of three-dimensional fast spoiled gradient recalled acquisition in the steady state (FSPGR) using ultra magnetic field 3-Tesla MRI for optimal pulse sequences of T1-weighted imaging. Nihon Hoshasen Gijutsu Gakkai Zasshi 62: 297-304.
20. Pruessner JC (2000) Volumetry of hippocampus and amygdala with high-resolution MRI and three-dimensional analysis software: Minimizing the discrepancies between laboratories. Cereb Cortex 10:
21. Ashburner J, Friston KJ (2000) Voxel-based morphometry-The methods. Neuroimage 11: 805-821.
22. Wang T (2014) The efficacy of plasma biomarkers in early diagnosis of Alzheimer's disease. Int J Geriatr Psychiatry 29: 713-719.
23. Gu Z (2005) Regulation of NMDA receptors by neuregulin signaling in prefrontal cortex. J Neurosci 25: 4974-4984.
24. Lee KH (2015) Bidirectional signaling of neuregulin-2 mediates formation of GABAergic synapses and maturation of glutamatergic synapses in newborn granule cells of postnatal hippocampus. J Neurosci 35: 16479-16493.
25. Tamura H (2012) Processing of neuregulin-1 by neuropsin regulates GABAergic neuron to control neural plasticity of the mouse hippocampus. J Neurosci 32: 12657-12672.
26. Yau HJ (2003) Neural development of the neuregulin receptor ErbB4 in the cerebral cortex and the hippocampus: Preferential expression by interneurons tangentially migrating from the ganglionic eminences. Cereb Cortex 13: 252-264.
27. Gajendran N (2009) Neuregulin signaling is dispensable for NMDA- and GABA (A)-receptor expression in the cerebellum *in vivo*. J Neurosci 29: 2404-2413.

28. Thuret S (2004) The neuregulin receptor, ErbB4, is not required for normal development and adult maintenance of the substantia nigra pars compacta. J Neurochem: 1302-1311.

29. Linying, Z (2014) Neuroprotective effects of neuregulin-1 ss on oligodendrocyte type 2 astrocyte progenitors following oxygen and glucose deprivation. Pediatr Neurol 50: 357-362.

30. Wen L (2010) Neuregulin 1 regulates pyramidal neuron activity via ErbB4 in parvalbumin-positive interneurons. Proc Natl Acad Sci 107: 1211-1216.

31. Jaworski A, Burden SJ (2006) Neuromuscular synapse formation in mice lacking motor neuron- and skeletal muscle-derived Neuregulin-1. J Neurosci 26: 655-661.

32. Mei L, Xiong WC (2008) Neuregulin 1 in neural development, synaptic plasticity and schizophrenia. Nat Rev Neurosci 9: 437-4352.

33. Gambarotta G (2004) ErbB4 expression in neural progenitor cells (ST14A) is necessary to mediate neuregulin-1 beta1-induced migration. J Biol Chem 279: 48808-48816.

34. Pitcher GM (2011) Schizophrenia susceptibility pathway neuregulin 1-ErbB4 suppresses Src upregulation of NMDA receptors. Nat Med 17: 470-478.

35. Hahn CG (2006) Altered neuregulin 1-erbB4 signaling contributes to NMDA receptor hypofunction in schizophrenia. Nat Med 12: 824-828.

36. Neddens J (2009) Neuregulin links dopaminergic and glutamatergic neurotransmission to control hippocampal synaptic plasticity. Commun Integr Biol 2: 261-264.

37. Pankonin MS (2009) Differential distribution of neuregulin in human brain and spinal fluid. Brain Res 1258: 1-11.

38. Sardi SP (2006) Presenilin-dependent ErbB4 nuclear signaling regulates the timing of astrogenesis in the developing brain. Cell 127: 185-197.

39. Liew H (2016) Soluble neuregulin-1 from microglia enhances amyloid beta-induced neuronal death. CNS Neurol Disord Drug Targets.

40. Chang KA (2016) Plasma soluble neuregulin-1 as a diagnostic biomarker for Alzheimer's disease. Neurochem Int 97: 1-7.