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The Potential of Neurogranin as a Prognostic Biomarker for Alzheimer's Disease

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Abstract:
Synaptic dysfunction is linked to cognitive symptoms in Alzheimer's disease. Thus, measurement of synapse proteins in cerebrospinal fluid (CSF) may be useful biomarkers to monitor synaptic degeneration. Neurogranin in cerebrospinal fluid correlates with cognitive decline and is a potential novel biomarker for Alzheimer disease (AD) dementia. This report compares three different studies that tested the ability of neurogranin to act as a biomarker for Alzheimer related decline in cognitive function and predicting the advancement of the disease by detecting synaptic loss. The first study was conducted within the memory clinic-based Amsterdam Dementia Cohort where it compared cerebrospinal fluid neurogranin of patients with Alzheimer's to that of controls with normal cognitive function it showed that baseline CSF levels of neurogranin in patients with AD were higher than in cognitively normal participants. The second study tested the performance of cerebrospinal fluid neurogranin to predict cognitive decline and brain injury in the Alzheimer's Disease Neuroimaging Initiative study. An in-house immunoassay was used to analyze neurogranin in cerebrospinal fluid samples from a cohort of patients who were diagnosed as having Alzheimer's disease with dementia or mild cognitive impairment, as well as in cognitively normal subjects, the results demonstrated that cerebrospinal fluid neurogranin is increased already at the early clinical stage of Alzheimer's disease and predicts cognitive deterioration and disease-associated changes over time. The third and final study was A cross-sectional and longitudinal observational study of cognitive decline in patients with symptomatic AD and cognitively normal controls, concluded that CSF levels of the synaptic marker neurogranin offer diagnostic and prognostic utility for early symptomatic AD that is comparable to other CSF markers. Also, CSF neurogranin complements the collective ability of these markers to predict future cognitive decline in cognitively normal individuals and, therefore, will be a useful addition to the current panel of AD biomarkers.

Introduction:
Alzheimer's is a type of dementia that causes problems with memory, thinking and behavior. Symptoms usually develop slowly and get worse over time, becoming severe enough to interfere with daily tasks, it is the most common cause of dementia, accounting for 60 percent to 80 percent of dementia cases. Alzheimer's disease is the sixth-leading cause of death in the United States, and the fifth-leading cause of death among those age 65 and older. It also is a leading cause of disability and poor health. [1] AD is characterized by pathological hallmarks including neuronal and synaptic degeneration and loss together with deposits of aggregated amyloid-β (Aβ) and tau. Increased CSF concentrations of protein tau reveal the ongoing cortical neurodegeneration while the typical Aβ plaque pathology in the AD brain is mirrored by decreased CSF levels of Aβ. The post-synaptic protein neurogranin has a pivotal role in long-term potentiation and learning, and while highly expressed in the brain, neurogranin is also present in CSF as a pool of several C-terminal fragments, with an intact or truncated C-terminus. Neurogranin (NGRN) is thought to be involved in activity-dependent synaptic plasticity and long-term potentiation through the modulation of calcium-mediated signaling pathways. Because of its abundant and preferential neuronal expression, neurogranin has been identified as a potential marker of neurodegeneration in large-scale gene arrays. [2] The aim of this study is using multiple studies to evaluate the potential of CSF neurogranin as biomarker for the early detection of synaptic degeneration in Alzheimer patients.

Discussion:

The first study was a Longitudinal study that included 163 patients in total; 37 cognitively normal participants, 61 patients with mild cognitive impairment (MCI), and 65 patients with AD. The results showed that Baseline CSF levels of NGRN in patients with AD (median level, 2381 pg/mL [interquartile range, 1651-3416 pg/mL]) were higher than in cognitively normal participants (median level, 1712 pg/mL [interquartile range, 1206-2724 pg/mL]). Baseline NGRN levels were highly correlated with total tau and tau phosphorylated at threonine 181 in all patient groups, but not with Aβ42. Baseline CSF levels of NGRN were also higher in patients with MCI who progressed to AD (median level, 2842 pg/mL [interquartile range, 1882-3950 pg/mL]) compared with those with stable MCI (median level, 1752 pg/mL [interquartile range, 1024-2438 pg/mL]), and they were predictive of progression from MCI to AD [2]

The second study conducted an in-house immunoassay was used to analyze neurogranin in cerebrospinal fluid samples from a cohort of patients who at recruitment were diagnosed as having Alzheimer's disease with dementia (n = 95) or mild cognitive impairment (n = 173), as well as in cognitively normal subjects (n = 110). Results showed that Cerebrospinal fluid neurogranin was increased in patients with Alzheimer's disease dementia, progressive mild cognitive impairment and stable mild cognitive impairment compared with controls, and in Alzheimer's disease dementia and progressive mild cognitive impairment compared with stable mild cognitive impairment. In the mild cognitive impairment group, high baseline cerebrospinal fluid neurogranin levels predicted cognitive decline as reflected by decreased Mini–Mental State Examination and increased Alzheimer's Disease Assessment Scale–cognitive subscale scores at clinical follow-up. Furthermore, within the progressive mild cognitive impairment group, elevated cerebrospinal fluid neurogranin levels were associated with accelerated deterioration in Alzheimer's Disease [3]

The third study aimed for correlations between baseline CSF biomarker levels and future cognitive decline in patients with symptomatic AD and cognitively normal controls overtime, and included a total of 302 individuals were included in this study 95 patients with AD and 207 controls. The CSF neurogranin levels differentiated patients with early symptomatic AD from controls with comparable diagnostic utility to the other CSF biomarkers, it correlated with brain atrophy in AD and with amyloid load in preclinical AD, and also neurogranin levels predicted future cognitive impairment. [4]

Conclusion:

In conclusion, Alzheimer's, is a chronic neurodegenerative disease that usually starts slowly and worsens over time, so a biomarker that predicts this progression can be very useful. The three studies mentioned above demonstrated the capability of neurogranin, a post-synaptic protein, to act as a biomarker for Alzheimer's, where increased levels of the protein in the CSF was observed in patients with Alzheimer's compared to controls and to other patients with less severe symptoms. Also, increased levels of neurogranin predicted the advancement of the disease.

References:

1. What Is Alzheimer's?. *Alzheimer's Disease and Dementia*. 2018. Available at: https://www.alz.org/alzheimers-dementia/what-is-alzheimers. Accessed June 27, 2018.
2. Kester M, Teunissen C, Crimmins D et al. Neurogranin as a Cerebrospinal Fluid Biomarker for Synaptic Loss in Symptomatic Alzheimer Disease. *JAMA Neurol*. 2015;72(11):1275. doi:10.1001/jamaneurol.2015.1867.

3. Portelius E, Zetterberg H, Skillbäck T et al. Cerebrospinal fluid neurogranin: relation to cognition and neurodegeneration in Alzheimer's disease. *Brain*. 2015;138(11):3373-3385. doi:10.1093/brain/awv267.
4. Tarawneh R, D'Angelo G, Crimmins D et al. Diagnostic and Prognostic Utility of the Synaptic Marker Neurogranin in Alzheimer Disease. *JAMA Neurol*. 2016;73(5):561. doi:10.1001/jamaneurol.2016.0086.