

Review Article

Assessment of Cerebrospinal Fluid Neurogranin as a Predictor of Alzheimer's Disease Through Synaptic Dysfunction

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Abstract: Cognitive changes in Alzheimer's diseases have been linked to synaptic degeneration and dysfunction. Hence, a biomarker of early synaptic defect like neurogranin, is clinically useful to enhance early diagnosis of the disease in susceptible individuals. This review assesses the various works done by various authors and researchers from various parts of the world on the role of neurogranin and its clinical usefulness in the early diagnosis of Alzheimer's disease, a degenerative brain disease with symptoms of progressive dementia. Using the internet and search engines as pubmed, google scholar, medline, index Copernicus etc, studies on Alzheimer's disease biomarkers and neurogranin were checked for to assess the conclusions of the researchers and also references of the retrieved articles were searched for further facts and information on the subject. Over the years, many researchers have been done to ascertain a suitable biomarker for Alzheimer's disease. The pathophysiological process of Alzheimer's is linked to synaptic degeneration and elevated cerebrospinal fluid neurogranin has been linked to this pathologic process. In this review, many authors find neurogranin a useful, accurate and reliable biomarker in the diagnosis and prognosis of Alzheimer's disease as neurogranin levels are elevated in patients with Alzheimer's disease when compared with controls. Elevated cerebrospinal fluid (CSF) levels of neurogranin is a promising biomarker of Alzheimer's diseases and tends to be clinically useful in early diagnosis and prognosis of the disease.

Keywords: Alzheimer's, Biomarkers, Pubmed, Neuropilin, Cerebrospinal Fluid, Synaptic

1. Introduction

NEUROGRANIN

Neurogranin, a calmodulin-binding protein, is majorly expressed in brain tissues and plays a role in protein kinase C signaling [1]. It is post synaptic protein regulating calcium availability. It is also called protein C substrate or RC3; and its gene, which is located on 11q24 encodes a post synaptic protein kinase substrate that binds calmodulin in the absence of calcium [1, 2]. High concentrations of neurogranin are found in the cerebral cortex, hippocampus, striatum and amygdaloid. These areas are gray matter – dominated and are affected by Alzheimer's disease [3]. Neurogranin has been studied extensively to assess its usefulness in the diagnostic workup

of patients with Alzheimer's disease. Its relevance in this regard is gaining grounds globally. This study aims at understudying its clinico-laboratory usefulness.

ALZHEIMER'S DISEASE (AD)

This is an irreversible, progressive, chronic degenerative disease of the brain which affects elderly people of whom most are over 65 years of age [4]. It is a rapidly progressive disease with affection of more than 36 million people globally [5]. The commonest risk factor for AD is increasing age, though earlier-onset AD can still occur. Other associated risk factors may be positive family history, genetic mutation, diabetes mellitus and previous history of head injury with

concussion. Its sex preponderance is on the female sex [5, 6].

It primarily causes about 70 – 80% of dementia-related illness in the elderly and initially manifests as short term memory, which later progresses to involve other symptoms such as behavioral changes, mood swings, disorientation and eventually death [5].

AD is characterized by pathological hallmark including neural and synaptic degeneration and loss, alongside with deposition of aggregated amyloid beta and tau protein. AD has been identified as a protein – misfolding disease characterized by neurofibrillary tangles, abnormally coded amyloid beta protein accumulated in plaques and tau protein in the brain [6-10].

2. Pathophysiology of Alzheimer's Disease

The synapse plays a major role in cognitive function, because it enhances neural transmission¹¹. It means that loss of synaptic innervations is the early pathological process of AD and this leads to eventual decline in cognitive function. Neuromodulin (GAP43) and neurogranin are two synaptic proteins. For this reason, neurogranin is therefore considered a biomarker for cognitive function. Levels of cerebrospinal fluid (CSF) neurogranin have been studied extensively as biomarker of synaptic loss and predictor of synaptic destruction [11, 12]. The CSF neurogranin concentration in AD relates to the total synapse density which is considerably reduced in AD. Again, the CSF concentration reflects an on-going synaptic loss – this causes continuous leakage of neurogranin into the brain interstitial fluid, which is cleared into the CSF resulting in higher CSF concentration. For this reason, concentration of neurogranin in the CSF of patients with AD are way higher than in healthy controls and so may reflect degeneration of synapses and a decline in cognitive function [11, 12].

3. Biomarkers of Alzheimer's Disease

Many neuro-chemical indicators/biomarkers have been proposed to assess early diagnosis of AD, and also to assess the progression of the disease. Several researchers over the years have proposed potential biomarkers such as beta amyloid (BA) [13, 14], total tau [15], tau phosphorylated at threonine 181 (P – tau 181) [16], cholesterol [17], 24 – hydroxycholesterol [17], 27 – hydroxycholesterol [17], β – site APP –clearing enzyme 1 gene (BACE1) [18], soluble precursor proteins (APP) [18], anti-beta amyloid antibodies [19] and neurogranin [20].

Over the past decades, many of these markers have found their way into clinical use and practice in assessing patients suspected to have AD. For instance, beta amyloid protein measurement may begin to show abnormalities more than 20 years before the overt symptoms of AD [14]. Also, a decline in CSF AB42 levels in mutation carriers relative to non-carriers begins about 25 years before symptoms of AD

appear [21]. Most of these biomarkers are obtained from CSF samples and may not reflect further functional decline because of their stability in patients with AD. And so far this reason, a biomarker with a capability to assess reduction in cognitive function – hence assessing neuronal synaptic loss is needed such biomarker as neurogranin. The synapse plays a major role in cognitive function, because it enhances neuronal transmission [11].

4. Neurogranin in Alzheimer's Disease

Several studies have been carried out to assess the correlation between CSF neurogranin levels and AD, especially its link in the prediction of cognitive decline in AD [11, 22-25].

Portelius E et al studied CSF neurogranin in relation to cognition and neuro-degeneration in AD. Since synaptic dysfunction is the major pathology linked to cognitive symptoms of AD. They measured CSF levels of neurogranin to monitor synaptic degeneration. A total 95 patients with dementia due to AD, and cognitive impairment due to AD (173 patients) and cognitively normal controls (110 people), they found that CSF neurogranin levels were elevated in the pre-dementia stage of the disease. CSF neurogranin was elevated in AD with dementia ($P < 0.001$), and mild cognitive when compared with control. These data show that CSF neurogranin is increases at an early clinical stage of AD and also predicts the progression of the disease [26].

Tarawneh R et al studied a total of 95 patients with symptomatic AD, and 207 apparently healthy controls (aged 73 years). It was found that those with symptomatic AD features had higher mean. CSF neurogranin level than those with non-AD dementia ($P < 0.001$) and correlated with brain atrophy. It was found that in assessing diagnostic accuracy of CSF neurogranin when composed with AD biomarkers the area under the land (AUC) with 0.71. They concluded that CSF neurogranin level is elevated during the preclinical period, and suggested cessation of increasing neurogranin levels through medication would indicate protection of nervous tissue [27].

Remnsted J et al studied 441 samples of patients with ventricular CSF collected post mortem and lumbar CSF and found elevated two synaptic proteins, neuromodulin (GAP 43) and neurogranin in CSF from AD patients in two independent cohort studies. They found increased levels of these two levels of these two proteins for whom the AD diagnoses was not established at the time of taking blood sample and propose their relevance in future diagnosis of AD [12].

Wellington H et al suggested that neurogranin is a specific biomarker for AD and not levels not seen in a range of other neurodegenerative disease. CSF neurogranin was higher on patients with AD composed to controls ($P < 0.001$) and all other disease groups ($P < 0.001$) [28].

In another study; Kester MI et al found that baseline CSF levels of neurogranin in patients, were higher than cognitively normal people and also the levels of neurogranin in patients

with mild cognitive impairment (MCI) who progressed to AD compared with stable MCI ($P=0.004$) [29].

Both Kvavilashvili H et al and Thorsell A et al and also found increased circulating CSF neurogranin patients with AD when compared with controls.

Reddy PH did a postmortem study on human tissues and it showed that levels of neurogranin were increased in AD [25]. Summarized findings of various researchers are illustrated on the table 1 below:

Table 1. Summarized findings of various researchers' on CSF neurogranin.

S/N	Author	Year of Study	Conclusion
1.	Portelius E et al [26]	2015	- CSF neurogranin levels were elevated in the pre-dementia stage of the disease. - CSF neurogranin was elevated in AD with dementia ($P<0.001$) - CSF neurogranin correlates with brain atrophy.
2.	Tarawneh R et al [27]	2016	- CSF neurogranin differentiates between early symptomatic AD from healthy controls with comparable diagnostic utility AUC = 0.71 (95 CI: 0.64 – 0.77) in relation to other biomarkers
3.	Kvavilashvili H et al [22]	2014	- CSF levels of neurogranin increased in patients with AD
4.	Thorsell A et al [11]	2010	- CSF levels of neurogranin are increased in patients with AD
5.	Reddy PH et al [25]	2005	- Post mortem studies of human tissue reflect that levels of neurogranin are increased in patients with AD. - CSF neurogranin is a special biomarker to AD and not seen in a range of other neurodegenerative diseases.
6.	Wellington H et al [28]	2016	- CSF neurogranin was higher in patients with AD compared to controls ($P<0.001$) and all other disease groups ($P<0.001$).
7.	Kester MI et al [29]	2015	- Baseline CSF levels of neurogranin in patients with AD were higher than control. - Neurogranin level is increased in patients who progressed to AD ($P = 0.004$).
8.	Remnestal J et al [29]	2016	- Both neurogranin and GAP 43 are found elevated in AD. - Both are relevant in early diagnosis of AD.

5. Laboratory Measurement of Neurogranin

The sample usually assayed for neurogranin is CSF obtained by lumbar puncture. This is then assayed by ELISA using sandwich immunoassay technique. It is a simple and accurate method. Plasma neurogranin does not correlate with AD as CSF neurogranin does²⁹. The pathological changes of AD come 20 – 30 years prior to onset of symptoms. Hence a biomarker of early detection/diagnosis is very important. Early symptoms of AD include synaptic change indicating neurogranin may be used as such a biomarker in diagnosis, prognosis and complement other biomarker to predict cognitive decline found in AD patients [29, 30, 31].

6. Conclusion

These studies tally with the fact that increased CSF neurogranin synchronizes with AD. Many various researchers concur to these. Furthermore, findings suggest that CSF neurogranin levels are elevated in AD. It is also known that in AD, amyloid beta selectively builds up in the mitochondria of AD – affected brain and inhibit certain enzyme function and the utilization of glucose. Hence a cluster of cognitive deterioration, decreased glucose metabolism and higher hippocampal atrophy define AD.

However, studies by Davidson P et al gives a century view – that CSF neurogranin levels are reduced in hippocampus and frontal lobes in patients with AD.

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