A literature review of AD7c-ntp as a biomarker for Alzheimer's disease

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Abstract

The cornerstone of diagnosis of Alzheimer's disease (AD) is still the clinical criteria for probable and possible AD established by the NINCDS-ADRDA Work Group in 1984, which had survived for over 27 years. However, with the increase in people's knowledge of clinical manifestations and biology of AD, this standard is gradually proving to be insufficient; the early diagnosis of AD is thus particularly important. Therefore, in 2011, the National Institute on Aging and the Alzheimer's Association revised the criteria and integrated biomarker evidence into it. Biomarker evidence is expected to enhance the pathophysiological specificity of the diagnosis of AD. According to Consensus Report of the Working Group on Molecular and Biochemical Markers of Alzheimer's Disease, a qualified biomarker for AD should have the following abilities: It should detect a fundamental feature of neuropathology and be validated in neuropathologically confirmed cases, reliably with an sensitivity >80% for detecting AD and a specificity >80% for distinguishing other dementias; be reproducible and non-invasive; and be simple to perform and inexpensive. Alzheimer-associated neuronal thread protein (AD7c-NTP) is a member of "neuronal thread proteins" (NTPs); it can be detected in increased concentration in cortical neurons, brain-tissue extracts, cerebrospinal fluid, and urine in the early course of AD neurodegeneration, and it level is proportional to the degree of dementia, which makes it a promising biomarker for AD. In this review, we have evaluated the feasibility of developing AD7c-NTP as a biomarker for AD.

Key Words

AD7c-NTP, Alzheimer's disease, biomarker, brain tissue extracts, cortical neurons, CSF, urine

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is characterized by cognitive and memory deterioration, progressive impairment of activities of daily living, and a variety of neuropsychiatric symptoms and behavioral disturbances.[1] By 2005, 24.2 million people worldwide had dementia,[2] in 2010, the number became 36.0 million, and it will continue to increase to 66 million by 2030 and 115 million by 2050;[3] approximately 70% of these cases were due to AD.[2] It is estimated that AD has a median prevalence of 4.8% and an annual incidence of 1275 per 100,000 in populations of individuals aged ≥ 60 years worldwide.[4] Women have a higher risk than men with a median men: women rate ratio of 0.54.[4] The social costs associated with AD are high; it is estimated that the global costs in 2010 was $604 billion,[3] with $172 billion in the USA alone.[5] In the new diagnostic guidelines for AD, AD was divided into three phases: The dementia phase (AD dementia due to AD); the symptomatic, pre-dementia phase (MCI due to AD); and the asymptomatic, preclinical phase of AD.[6] The first two phases are intended to guide diagnosis in the clinical setting, and the preclinical phase is intended purely for research purposes. However, there are still no effective treatments to prevent, halt, or reverse AD, the only therapies available for AD were to postpone or alleviate the condition.[7] Therefore, the early diagnosis of AD is very important.

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NTP

Neuronal thread proteins (NTP) are a family of molecules expressed in the brain and the neuroectodermal tumor cell lines; the NTP expression is increased in neuronal cells during proliferation, differentiation, brain development, and AD neurodegeneration.[8] Previous researches have shown that the 15-18-kD NTP cluster is associated with the development and neuronal differentiation, whereas the 21 kD and 39-42 kD species are overexpressed in AD, correlating with neurodegenerative sprouting and synaptic disconnection.[8] A research has also shown that NTP immunoreactivity and

higher concentrations of proteins in the cerebral tissue were significantly correlated with AD diagnosis and abundant neurofibrillary tangles.[9]

AD7c-NTP

In 1997, de la Monte *et al*., isolated a novel Alu sequence-containing cDNA, over-expressed in an AD brain expression library, designated AD7c-NTP.[10] AD7c-NTP is an approximately 41-kD brain protein present in the long axonal processes that emerge from the nerve cell body, is associated with the pathological changes of AD, and is selectively elevated in the AD brains.[11,12] *In vitro* studies demonstrated that over-expression of AD7c-NTP in transfected neuronal cells promotes neuritic sprouting and cell death, the two principal neuroanatomical lesions correlated with dementia in AD.[10] De la Monte *et al*., indicated that the abnormal AD7c-NTP expression is associated with AD neurodegeneration and that, during the early stages of the disease, the CSF levels correlate with the severity of dementia.[10] Ghanbari *et al*., found that the AD7c-NTP immunoreactive proteins detected in urine have the same molecular mass as the proteins detected in human CSF and cerebral tissue and that both the tests have similar accuracy for the diagnosis of AD.[13] In this review, we have summarized the related clinical trials to describe the current status of AD7c-NTP as a diagnostic tool for AD.

AD7c-NTP in the Diagnosis of Alzheimer's Disease

AD7c-NTP is detected in increased concentration in the cortical neurons, brain-tissue extracts, cerebrospinal fluid, and urine early in the course of AD neurodegeneration,[14] and its level is positively correlated with the severity of dementia. All these characteristics make it a possible biomarker for AD.

AD7c-NTP in CSF

De la Monte's study showed that, in postmortem CSF, the mean concentration of AD7c-NTP in cases of definite AD was higher than that in the age-control group, and, in the CSF samples from individuals with early possible or probable AD, the mean concentration of AD7c-NTP was also elevated relative to the levels in CSF from age-matched and neurological disease controls.[10] AD7c-NTP levels in CSF were positively correlated with the severity of dementia rather than with age or the duration of disease, which may mark AD neurodegeneration process.[10] In 1998, Ghanbari *et al*., developed a new immunoassay called AD7c test to detect and measure CSF AD7c-NTP.[15] Their assay was highly sensitive, linear to 2.0 ng, the sensitivity and specificity were both 89%, which had similar result with de la Monte's trial. Ghanbari's subsequent study once more supported the above views (specificity 94% and sensitivity 83%) and clearly confirmed the specificity of AD7c-NTP as a biomarker of AD.[16]

AD7c-NTP in urine

In 1998, Ghanbari's study demonstrated that the AD7c-NTP immunoreactive proteins in urine have the same molecular mass as in CSF and cerebral tissue, and both tests have similar accuracy.[13] A competitive enzyme-linked immunosorbent assay (ELISA) tested in urine samples showed that the mean assay measurement in the AD group was significantly higher than that in the non-AD dementia control group, and, in the non-dementia control group, the mean assay measurement in early AD cases was significantly lower than that in other AD cases.[12] A new configuration of the AD7c-NTP assay, termed "7c Gold" suggested that AD7c-NTP is an excellent biomarker that can be helpful in routine clinical evaluation of elderly patients at risk for AD.[17] Nowadays, urine AD7c-NTP diagnostic kit has been developed, which is reproducible and has high sensitivity and specificity for the diagnosis of AD.[18]

AD7c-NTP combined with tau in CSF

In 2000, Kahle *et al*., conducted a test to compare the CSF levels of tau and AD7c-NTP in patients with AD and in control subjects.[19] In their study, CSF tau had 63% sensitivity and 89% specificity, while AD7c-NTP had 70% sensitivity and 87% specificity for diagnosis of AD; combined evaluation of both biomarkers with discriminant analysis raised the specificity to 93% at a 63% sensitivity level. De la Monte indicated that AD7c-NTP over-expression may have a direct role in mediating some of the important cell death cascades associated with AD neurodegeneration, and further established a link between AD7c-NTP overexpression and the accumulation of phospho-tau in preapoptotic CNS neuronal cells.[20] Over-expression of AD7c-NTP was associated with increased levels of phospho-tau, but not with amyloid-beta immunoreactivity.

Problems with AD7c-NTP

AD7c-NTP has high sensitivity and specificity for the diagnosis of AD, and urine test has similar accuracy with CSF test. Moreover, its non-invasive and simple characteristics make it acceptable in clinic. However, there exist several problems to be detected and resolved.

Exclusion and inclusion criteria for the urine samples: Cloudy and highly colored samples were excluded, and the clear samples were sent for routine urinalysis. Samples with any of the following abnormalities were rejected: (a) protein (24 h) <40 mg or >200 mg; (b) presence of any significant numbers of white blood cells, red blood cells, or bacteria; (c) crystalluria; (d) abnormal specific gravity; (e) abnormal pH; (f) presence of glucose, ketones, nitrites, bilirubin, or urobilinogen.[13]

The separation and purification of AD7c-NTP is a difficult problem; further research is required for the same without pure protein.[21] A human gene cDNA cloned from the human fetal brain cDNA library termed "PDLIM5" was found to be homologous to AD7c-NTP.[22] RT-PCR experiment revealed that the expression level of PDLIM5 in the brain, skeletal muscles, prostate, colon, and leukocyte is obviously higher than that in other tissues. However, the relationship between AD7c-NTP and PDLIM5 and the significance of the presence of PDLIM5 remains unclear.

Conclusion

AD7c-NTP increases in cortical neurons, brain-tissue extracts, cerebrospinal fluid, and urine in the early course of AD, and its level is positively correlated with the severity

of dementia, which make it a potential biomarker for AD. Urine AD7c-NTP test is non-invasive, and the development of urine AD7c-NTP diagnostic kit makes it more convenient to implement. When combined with other biomarkers, such as tau, it will provide a higher diagnostic accuracy. Further studies should be conducted to explore the relationship between AD7c-NTP with other biomarkers, for example, Aβ, estrogen, matrix metallo proteinases, and F (2)-isoprostanes. However, few researches about the physiological and pathophysiological functions of AD7c-NTP state that its mechanism of action in AD degeneration is still unknown. To understand this, scientific efforts should be intensified in addition to broadening and deepening the understanding of AD pathobiology.

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