

# Enzyme BACE1 may be important in predicting onset of Alzheimer disease

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The critical enzyme beta-secretase1 (BACE1) is known to be elevated in brains with sporadic Alzheimer disease (AD). Scientists have now found increased levels of BACE1 in brains with mild cognitive impairment (MCI), suggesting that BACE1 activity is important for conversion of mild cognitive impairment to AD and may be an early indicator of AD. The results are published in the January issue of *The American Journal of Pathology*.

Understanding the early events of AD is key to effective diagnosis and treatment. Two of the major pathological characteristics of AD are neuritic plaques and neurofibrillary tangles, which are used to diagnose or confirm AD at autopsy. Neuritic plaques, which are also known as senile, dendritic, or amyloid plaques, consist of deteriorating neuronal material surrounding deposits of a sticky protein called [amyloid beta peptide](#) (A $\beta$ ). Neurofibrillary tangles consist of highly phosphorylated forms of the microtubule-associated protein tau.

Following on earlier discoveries that BACE1 activity and protein expression are significantly increased in AD brains, researchers have now found raised levels of BACE1 [enzymatic activity](#) in [brain tissue](#) from patients with MCI, a precursor to AD. BACE1, also known as  $\beta$ -site [amyloid precursor protein](#) cleaving enzyme, is an aspartic protease and is a critical enzyme that promotes A $\beta$  generation.

In the current study, researchers examined autopsied brain tissue from 18 patients with clinically well-characterized AD, 18 patients with MCI,

and 18 non-demented patients. They found that BACE1 enzymatic activity was significantly increased in both MCI and AD brains. In 11 of 18 MCI patients, who had undergone a mini-mental state examination (MMSE) before death, the brain cortex BACE1 levels increased during early dementia followed by a precipitous decrease as the decline in cognition progressed. Increased BACE1 activity correlated with plaque numbers and cognition status. Interestingly, they also observed that there was no significant difference in BACE1 activity between MCI and AD.

The researchers also found an increase in tumor necrosis factor alpha (TNF $\alpha$ ) in MCI brains. TNF $\alpha$  is an inflammatory cytokine or cell signaling protein required for amyloid protein induced neuronal death. Biochemical examination of the autopsy tissue showed that TNF $\alpha$  rather than other cytokines increases the response to BACE1 [protein expression](#). The increased levels of TNF $\alpha$  in MCI and AD patients were not significantly different from each other.

"There is more and more evidence that BACE1 is intricately involved in the development of AD," says the study's lead investigator Yong Shen, PhD, of the Center for Advanced Therapeutic Strategies for Brain Disorders at Roskamp Institute, Sarasota, Florida. "Our previous studies have demonstrated elevated BACE1 enzymatic activity in AD brains and in the cerebrospinal fluid from MCI and AD patients. Our findings here suggest that BACE1 increases early in the course of MCI and is possibly induced by inflammatory molecules like TNF $\alpha$  and that BACE1 enzymatic activity may be important for conversion of MCI to AD. Importantly, we found that the BACE1 activity in tissue from people with MCI was significantly increased by 27%, compared with that from people with no dementia.

"We believe that BACE1 activity precedes the clinical diagnosis of AD and could be an early indicator of neuronal dysfunction or pathology in AD. Moreover, it may be a good therapeutic target for AD, as evidenced

by recent promising clinical trials on BACE1 inhibitors," he concludes.

**More information:** "High Activities of BACE1 in Brains with Mild Cognitive Impairment," by Xin Cheng, Ping He, Taehee Lee, Hailan Yao, Rena Li, Yong Shen ( [dx.doi.org/10.1016/j.ajpath.2013.10.002](https://doi.org/10.1016/j.ajpath.2013.10.002) ), *The American Journal of Pathology*, Volume 184, Issue 1 (January 2014)

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