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# PLASMA β-SECRETASE1 (BACE1) LEVELS AS MARKER OF COGNITIVE FUNCTION DECLINE IN ELDERLY

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**Abstract.** *BACE1 which forms amyloid plaques consisting of amyloid β peptides is a typical neuropathological lesion in the brain of Alzheimer's disease. Many studies have shown that β-amyloid is central to the pathophysiology of Alzheimer's disease and may play an early role in neurodegenerative disorders. The BACE1 enzyme forms amyloid β plaques. The BACE1 protein is detectable in plasma and its levels are significantly increased in patients with mild cognitive impairment and future Alzheimer's. This Aβ peptide accumulates into senile plaques causing the characteristics of Alzheimer's disease, can cause neuronal death and cognitive decline*

**Keywords: Gene, BACE1, Elderly**

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## 1 Introduction

Currently, Indonesia is entering a period of an aging population, which is marked by an increase in life expectancy followed by an increase in the number of elderly people. In 2025 it is estimated that the number of elderly people will increase to 36 million people [28]. The number of elderly

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people in Indonesia continues to increase from year to year. In 1990 there were 6% in of the elderly. In 2020 it will be 9.3% and it is projected that it will continue to increase to 16% in 2050. Thus it is projected that by 2045, the elderly population in Indonesia will make up almost one-fifth of the total population [3].

One of the problems encountered by the elderly is impaired cognitive function, cognitive impairment in the elderly that begins with mild cognitive impairment varies, consisting of mild amnestic cognitive impairment, non-amnestic mild cognitive impairment, and multi-dominant mild cognitive impairment which will develop into dementia [31]. Amnestic mild cognitive impairment is hypothesized to progress to Alzheimer's disease if there is an underlying degenerative etiology. Amnestic mild cognitive impairment can develop into non-Alzheimer's dementia such as frontotemporal dementia if one domain is affected by a degenerative etiology [27].

Cognitive impairment has an impact on functional abilities and care needs in the elderly. Mild cognitive impairment is diagnosed by the presence of impairment in one or more cognitive domains without meeting the diagnostic criteria for dementia. Nearly 16% of the elderly experience mild cognitive impairment without developing dementia. This is more often found in men than women. Statistical results from mild cognitive impairment to Alzheimer's disease range between 12% and 15%, compared to 1-2% in healthy adults [51].

The cognitive disorder is an important health problem because it will have an impact on the social and economic life of the community. Research in China on changes in cognitive function and risk factors for cognitive impairment in the elderly is still rare. China has become the fastest-growing country in the world for people with a population scale of cognitive impairment. Elderly with mild cognitive impairment may experience cognitive dysfunction, whereas those with severe cognitive impairment may develop dementia or Alzheimer's disease, resulting in loss of capacity to complete daily routines and result in an inability to live independently [55]. Whereas in research in Indonesia from a statistical agency, the number of elderly people will increase every year [3].

## 2. Factors affecting BACE1

Factors that negatively affect cognitive function include brain damage from cerebral ischemia, head trauma, toxins such as alcohol, stress hormone excess, or the development of degenerative dementias such as Alzheimer's. Factors of a negative impact can cause cumulative damage to the brain with age and result in cognitive impairment. Degenerative dementia is the most common cause of cognitive decline [26]. Figure 1 regarding the differences in the brains of healthy people and brains with Alzheimer's [2].

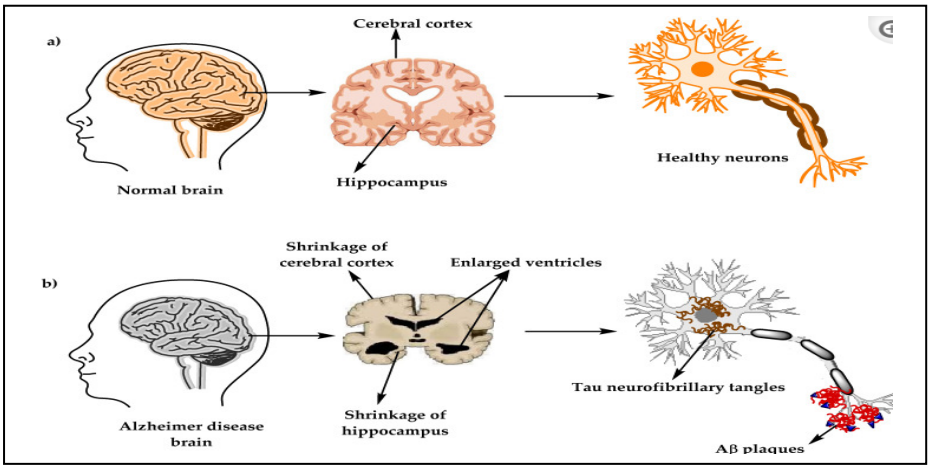



Figure 1: (a) the brain of a healthy person (b) the brain that has Alzheimer's [2].

## 3. Structure and Function of the BACE1 Protein

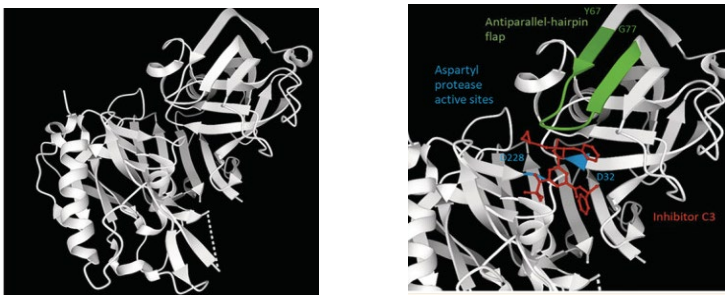
BACE1 is a membrane-bound enzyme from the pepsin family and can cleave the peptide bonds of aspartic and glutamic acids from amyloid precursor proteins [6].

BACE1 is a type 1 membrane protein that, together with BACE2, forms a subfamily of membrane aspartyl proteases [53]. BACE1 was first synthesized in the endoplasmic reticulum as an immature amyloid precursor protein (proBACE1) with a molecular mass of 60 kDa (kiloDalton). The BACE1 gene spans 30 kilobases (kb) on the human chromosome (11q23.2) and spans 9 exons. The BACE-1 gene promoter lacks the typical CAAT and TATA boxes, but the BACE1 gene contains six unique functional domains and three structural domains with sequence complexity preceded by the ATG start codon. Beta-site amyloid precursor protein cleaving enzyme-1 (BACE1) has historically focused on the brain and its action as a β-secretase responsible for the production of amyloid beta peptide (Aβ). This Aβ peptide accumulates into senile plaques causing the characteristics of Alzheimer's disease, which can cause neuronal death and cognitive decline [7]. The BACE1 gene is transcribed as a 501 amino acid preprotein, which contains five key domains, a signal peptide, and pro-catalytic, transmembrane, and cytoplasmic domains. The signal peptide delivers the BACE1 preprotein to the endoplasmic reticulum, where furin cleavage of the pro-domain results in the mature BACE1 protein [47]. The transmembrane domain determines the localization of BACE1 to the Golgi end, within the trans-Golgi network BACE1 is activated post-translation. BACE1 protease activity is dependent on the two aspartyl active sites at D93 and D289, as well as the position of the regulatory antiparallel hairpin flap relative to the substrate-binding site.

The activated BACE1 protein then operates on the plasma membrane in endosomes and the functioning Golgi apparatus at an optimal pH of 4.5 [37].

The BACE1 enzyme catalyzes the cleavage of Amyloid Precursor Protein (APP) to produce soluble amyloid precursor protein (sAPPß). The last peptide is then cleaved by ß secretase to form the amyloid 42 (Aß 42) peptide fragment. ß secretase and γ secretase form the amyloid

42 peptide fragment (Aß 42). After that, 42 amyloid ß collects and forms senile plaques, senile plaques which are the main neuropathological features of Alzheimer's disease [4]. Amyloid β peptides exist in two forms, namely 40 or 42 amino acids [6].




(a) (b)

Figure 2: BACE1 structure. BACE1 crystal structure images were generated using the 3TPR structure using the RSCB Protein Data Bank (https://www.rcsb.org/). (a) Structure without annotations (b) Structure of the C3 inhibitor binding (red), the two aspartyl protease active sites (blue) at D93 and D289, and the hairpin-antiparallel flap (green) between Y128–G138 shown (right). The structure of 62 residues is lost [38].

**4. BACE1 Substrates and Functions**

BACE1 is focused on its role in the amyloidogenic pathway, BACE1 is responsible for the early cleavage of the rate-limiting protein APP. Sequential cleavage by BACE1 and γ-secretase yields the Aβ-40 and Aβ-42 peptides. Despite having approximately 64% homology with BACE1, BACE2 cleaves the APP protein at alternative sites and therefore does not produce the same β-secretase action and Aβ production [44]. BACE2 is also mainly found in peripheral tissues, in contrast to BACE1 which is widely expressed in the brain [1]. BACE1 Aβ-42 production is associated with memory regulation, synaptic function, myelin repair, and Alzheimer's [42]. Alzheimer's is the most common dementia and presents with several physiological changes besides the accumulation of Aβ-42 into extracellular amyloid plaques, including neurofibrillary tangles (NFTs), chronic inflammation, loss of synapses, neuronal death, and hypometabolism [11 and 19]. Accumulation of Aβ plaques interfere with nerve and synaptic function which causes cognitive impairment effects [43]. BACE1 is involved in various metabolic functions [20, 24, and 25]. The physiological role of BACE1 in different cells and organelles, in addition to its role in Alzheimer's. Although the expression of BACE1 is highest in the brain, more is expressed, in other tissues it is lower including endocrine tissue, pancreas, muscle tissue, respiratory tissue, bone marrow, and lymphoid tissue. Because APP is also widely expressed BACE1-mediated Aβ production can have effects on many cells and tissues [42]

## 5. BACE1 as a marker of impaired cognitive function

Single Nucleotide Polymorphism (SNP) polymorphism of the BACE1 gene can affect the expression of the BACE1 gene and the activity of the BACE1 gene. The BACE1 gene is located on chromosome 11 (11q23.3) and appears to have a genetic variation that can lead to the risk of Alzheimer's disease. SNP can also create phenotypes, there are 23 locations to create polymorphisms, therefore SNP can determine whether a patient is at risk for Alzheimer's disease [50]

A Sampling of BACE1 through blood with plasma sampling. BACE1 as a marker of impaired cognitive function. The BACE1 protein is detectable in plasma and its levels increase significantly in patients with mild cognitive impairment and will become Alzheimer's [35]. The optimal value of BACE1 levels is 20.7 kU/L [5].

## 6. Conclusion

BACE1 levels in plasma can be used as a marker of cognitive function

## 7. Suggestion

With this information, BACE1 is used as a screening tool to determine the risk of cognitive impairment so that health workers take preventive measures

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