Increased Plasma Beta-Secretase 1 May Predict Conversion to Alzheimer’s Disease Dementia in Individuals With Mild Cognitive Impairment

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ABSTRACT

BACKGROUND: Increased beta-secretase 1 (BACE1) activity has consistently been detected in brain tissue and cerebrospinal fluid of subjects with mild cognitive impairment (MCI) and probable Alzheimer’s disease (AD) compared with control subjects. The collection of cerebrospinal fluid by lumbar puncture is invasive. We sought to identify the presence of plasma BACE1 activity and determine potential alterations in subjects with MCI with clinical follow-up examinations for 3 years using patients with diagnosed probable AD dementia compared with healthy control subjects.

METHODS: Seventy-five patients with probable AD, 96 individuals with MCI, and 53 age-matched and sex-matched healthy control subjects were recruited from three independent international academic memory clinics and AD research expert centers. Plasma BACE1 activity was measured by a synthetic fluorescence substrate enzyme-linked immunosorbent assay. BACE1 protein expression was assessed by Western blotting using three different antibodies that recognize the epitopes of the N-terminus, C-terminus, and full-length BACE1.

RESULTS: Compared with healthy control subjects, plasma BACE1 activity (V_{max}) significantly increased by 53.2% in subjects with MCI and by 68.9% in patients with probable AD. Subjects with MCI who converted to probable AD dementia at follow-up examinations exhibited significantly higher BACE1 activity compared with cognitively stable MCI nonconverters and showed higher levels of BACE1 activity than patients with AD.

CONCLUSIONS: Plasma BACE1 activity is significantly increased in MCI converters and patients with probable AD. The sensitivities and specificities of BACE1 activity for the patients were 84% and 88%, respectively. Our results indicate that plasma BACE1 activity may be a biomarker for AD risk and could predict progression from prodromal to probable AD dementia.

Keywords: Alzheimer’s disease dementia, BACE1, β-secretase, Biomarker diagnosis, Mild cognitive impairment, Prediction

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Blood BACE1 Activity Predicts AD in MCI Subjects

The increased BACE1 enzymatic activity and protein concentrations in CSF provides biological evidence of identifying preclinical stages of AD in individuals with MCI compared with age-matched and sex-matched healthy control (HC) subjects (24). The interaction of CSF BACE1 activity with established core CSF biomarkers Aβ1-42, Aβ1-40, total tau (t-tau), and tau phosphorylated at threonine 181 (p-tau181) has been previously investigated (34). Moreover, BACE1 activity was significantly elevated in APOE ε4 carriers compared with APOE ε4 noncarriers and correlated with CSF concentrations of Aβ1-40, t-tau, and p-tau181, thus indicating that greater BACE1 activity in CSF is dynamically linked to underlying AD brain pathology and disease severity (24,34,35). Furthermore, CSF BACE1 activity is one of the strongest predictors of AD risk compared with other biomarker candidates, such as brain atrophy (revealed via magnetic resonance imaging–based hippocampal volume reduction) and CSF concentrations of t-tau, p-tau181, Aβ1-42 as well as APOE status or age (36).

In addition to CSF biomarkers, which necessitate invasive lumbar puncture procedures (37,38), potential biomarkers for AD risk that can be obtained from more accessible sources such as blood (plasma/serum) are required. An ideal biomarker will need to be directly related to the disease pathogenesis in the brain. From this viewpoint, BACE1 is thought to be a relevant biomarker. To our knowledge, no data have been published on peripheral BACE1 expression and activity in HC subjects, individuals with MCI, and patients with AD. Therefore, in the present study, we sought to investigate BACE1 activity and protein expression in plasma samples of HC subjects, individuals with MCI (converters vs. nonconverters), and patients with probable AD dementia. We found that plasma concentrations of BACE1 are able to stratify the clinically relevant diagnostic subgroups mentioned above at baseline and predict the progression and conversion of MCI to overt AD dementia.

METHODS AND MATERIALS

Participants
From three independent international academic AD research centers and memory clinics, 224 individuals were recruited: 131 from the Department of Psychiatry and Psychotherapy, Alzheimer Memorial Center, Ludwig-Maximilian University, Munich, Germany; 68 from the Department of Neuroscience and Physiology, University of Gothenburg, Sahlgrenska University Hospital, Mölndal, Sweden; and 25 from the Memory Center, Roskamp Institute, Sarasota, Florida. Three age-matched multisite study cohorts were assembled: 75 probable AD patients, 96 MCI individuals, and 53 age-matched and sex-matched HC subjects. No age differences were found among the three groups using a generalized linear model. In accordance with previously published BACE1 studies (24,35), the diagnosis of probable AD was made according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association criteria, including the Mini-Mental State Examination (MMSE) score (39,40). MCI was diagnosed according to the Petersen criteria (33). MCI individuals performed 1.5 SD below the age-adjusted reference average in memory scales using the Consortium to Establish a Registry for Alzheimer’s Disease cognitive battery (41). HC subjects were represented by age-matched cognitively and physically healthy individuals. Patients with psychiatric comorbidity were excluded by history, clinical examination, and Composite International Diagnostic Interview (42). We obtained the clinical data from three independent centers where individuals with probable AD and MCI, including cognitively stable individuals with MCI and individuals with MCI who converted to AD, were enrolled. In all clinical centers, the stable MCI group was followed clinically for 2 to 3 years, while follow-up of MCI converters continued until conversion to AD dementia.

Blood BACE1 Activity Predicts AD in MCI Subjects

All blood samples were handled in an identical fashion, including coding, centrifugation, plasma extraction, and storage conditions. The maximum delay between blood drawing and centrifugation was 1 hour; each plasma sample was stored in a –80°C freezer until assayed in duplicate for BACE1 activity. All measures were performed blinded to the clinical status of the study participants.

BACE1 activity assays were performed as previously described with minor modifications (24). In brief, synthetic peptide substrates containing the β-cleavage site (Calbiochem; EMD Chemicals, Inc., Gibbstown, NJ) at a 10 μmol/L concentration in reaction buffer (50 μmol/L acetic acid buffer, pH 4.5, 100 μmol/L sodium chloride) were used for BACE1 activity assay. Ten microliters of plasma was mixed with 100 μL of buffer with the final pH of approximately 4.5, which is optimal for the BACE1 activity assay. The fluorescence was measured at 430 nm (excitation wavelength) and 520 nm (emission wavelength). BACE1 activity was corrected by plasma total protein content and calculated through Vmax and Vmean as previously described (24) and expressed in fluorescence units/time. Plasma BACE1 activity was tested in the presence of β-Secretase Inhibitor IV (EMD Chemicals, Inc.), while recombinant BACE1 peptide (Sigma-Aldrich, St. Louis, MO) was used as positive control during the assay. The inhibition ratio was obtained by the following equation: Inhibition (%) = (1 – S/C) × 100, where C indicates the plasma BACE1 activity in the absence of β-Secretase Inhibitor IV, and S indicates the plasma BACE1 activity in the presence of different concentrations of β-Secretase Inhibitor IV. The half maximal inhibitory concentration (IC50) value was calculated using GraphPad Prism 5 software (GraphPad Software, Inc., La Jolla, CA). To confirm the specificity of plasma BACE1 activity, we coated a 96-well plate with the BACE1 specific antibody MAB5308 (1:4000; EMD Millipore, Billerica, MA) to capture the BACE1 protein, and then we measured BACE1 activity.
Blood BACE1 Activity Predicts AD in MCI Subjects

**BACE1 Western Blot Assay**

For Western blot analysis, plasma samples were mixed with an equal volume of sodium dodecyl sulfate sample buffer and separated using a 10% sodium dodecyl sulfate polyacrylamide gel. The protein was then transferred to the nitrocellulose membrane. The membrane was stained with 1% Ponceau S staining solution as loading control, and brain lysates of AD patients were utilized as positive controls. The membrane was then probed with anti-BACE1 N-terminus (B0681; Sigma-Aldrich), C-terminus (B0806; Sigma-Aldrich), or ectodomain monoclonal antibody (MAB931; R&D Systems, Minneapolis, MN). Ponceau S staining solution (Sigma-Aldrich) was used as loading control. Intensities of protein bands were determined using Quality One 1-D Analysis Software (Bio-Rad Laboratories, Inc., Hercules, CA).

**Statistical Analysis**

Appropriate descriptive statistics including mean, SD, median, and range were computed in presenting the overall data. Generalized linear models were fitted with multiple comparison tests to compare diagnostic groups and other categorical predictors for each of the outcome measures, including BACE1 protein expression, BACE1 activities, total protein concentrations, and BACE1 activity/MMSE values. These models allowed us to account for age effects without inflicting the type I error level, while simultaneously adjusting for key factors. The data, including correlation in each diagnostic group, were analyzed using SPSS version 11.5.1 (SPSS Inc., Chicago, IL).

**RESULTS**

**Detection of BACE1 Protein Expression and Enzymatic Activity in Human Plasma**

To investigate whether BACE1 protein could be detected in plasma, a specific anti-BACE1 N-terminus antibody was utilized. We found that plasma samples contained BACE1 protein at the expected size, approximately 70 kD (Figure 1A), similar to that found in the human brain and CSF (16,17,24). A fluorogenic APP-derived peptide was employed as a BACE1 substrate to examine BACE1 specific activity, with BACE1 APP-derived peptide substrate used as a positive control. Plasma BACE1 enzymatic activity was inhibited by a specific BACE1 inhibitor (IC\textsubscript{50} dose at approximately 14 nmol/L) (Figure 1B and C). In our study, the IC\textsubscript{50} dose of 14 nmol/L necessary for inhibiting BACE1 is significantly different from the IC\textsubscript{50} of both BACE2 and cathepsin D (43). These findings indicate that BACE1 protein is detectable via enzyme-linked immunosorbent assay methods, and its enzymatic activity is abundant in human plasma.

**Investigation of Plasma BACE1 Activity in MCI Individuals and AD Patients at Different Stages**

MCI converters (n = 71) and AD patients (n = 75) showed significantly higher BACE1 activity compared with HC subjects (n = 53) and MCI nonconverters, which increased V\textsubscript{max} by 62.8% (p = .001) and 68.9% (p < .001) in MCI converters and AD patients, respectively (Figure 2A). Compared with HC subjects, the V\textsubscript{mean} of BACE1 activity in MCI nonconverters, MCI converters, and AD patients increased by 45.0% (p < .05), 85.4% (p = .001), and 97.3% (p < .001) (Figure 2A). The results of the generalized linear model supported the fact that the association of increased peripheral BACE1 activity with both AD patients and MCI converters is valid. There was no significant difference in BACE1 activity between MCI individuals and AD patients for V\textsubscript{max} (p = .756) and V\textsubscript{mean} (p = .8). To validate the increased plasma BACE1 activity in MCI converters and AD patients (Figure 2A) compared with HC subjects, we used an anti-BACE1 antibody to precipitate the protein and measured the enzymatic activity of the antibody-captured protein. Again, there was elevated enzymatic activity.
was also a significant correlation detected between activity and protein expression of BACE1 in HC subjects and MCI nonconverters versus MCI converters and AD patients (Figure 2C). Elevated BACE1 activities in both MCI converters and AD patients are also highly associated with disease-specific proteins tau and Aβ1–42 concentrations in CSF (Figure 3A–C). Moreover, BACE1 activities were associated with disease progression as measured by MMSE (Figure 4A).

Effects of Sex on Plasma BACE1 Activity in MCI Individuals and AD Patients

Based on the generalized linear model for $V_{\text{max}}$, we found that BACE1 activity belonging to MCI nonconverters, MCI converters, and AD patients increased in women by 67.2% ($p < .06$), 105.7% ($p = .012$), and 100.2% ($p < .001$), respectively, compared with women in the HC group (Supplemental Figure S3A). In men, plasma BACE1 $V_{\text{max}}$ activity in MCI nonconverters, MCI converters, and AD patients was increased by 10.8% ($p > .05$), 40.8% ($p = .033$), and 59.3% ($p = .012$), respectively, compared with men in the HC group (Supplemental Figure S3A). The $V_{\text{mean}}$ values of plasma BACE1 activity showed similar sex differences; in women, $V_{\text{mean}}$ BACE1 activity in MCI nonconverters, MCI converters, and AD patients increased by 26.2% ($p > .05$), 59.5% ($p = .007$), and 85.5% ($p = .013$), respectively, by setting the enzymatic activity as a reference in the corresponding male HC group (Supplemental Figure S3B). No significant sex differences were found in terms of BACE1 activity between HC subjects, MCI individuals, and AD patients (Supplemental Figure S3C). The generalized linear model showed an association of plasma BACE1 activity with the clinical diagnosis, after adjusting for sex ($p = .0002$) (Table 1). No statistically significant associations were observed between BACE1 activity and age ($p = .6258$) or sex ($p = .1582$) (Table 1) as well as centers ($p = .7670$).

Validation of Plasma BACE1 Activity Compared With Established Core CSF AD Biomarkers and Cognition

As plasma activity of BACE1 increased in MCI individuals and AD patients compared with HC subjects, MCI nonconverters, MCI converters, and AD patients (Figure 2A), we validated BACE1 activity as a plasma biomarker candidate by comparing the established CSF predictors for progression or conversion to dementia, tau protein and Aβ1–42 peptide (44,45), with plasma BACE1 activity and found a significant correlation (Figure 3A). In the MCI group, correlational analysis further revealed a significant positive correlation between BACE1 activity and CSF tau concentrations ($r = .45$; $p < .05$) (Figure 3B) and an inverse correlation between BACE1 activity and CSF Aβ1–42 concentrations ($r = .29$; $p > .05$) (Figure 3C). Similarly, in the AD group, we observed a significant correlation between BACE1 activity and CSF tau concentrations ($r = .50$; $p < .05$) (Figure 3C) and an inverse correlation between BACE1 activity and CSF Aβ1–42 concentrations ($r = .70$; $p < .01$) (Figure 3C). In contrast, in the HC group,

![Figure 2](image_url)

Figure 2. Beta-secretase 1 (BACE1) enzymatic activity and protein expression in plasma samples from healthy control (HC) subjects, mild cognitive impairment (MCI) individuals, and Alzheimer’s disease (AD) patients. The activity of BACE1 was measured by using synthetic peptide substrates containing the BACE1 cleavage site as we reported (17) with modifications. (A) BACE1 activity as a percentage of the HC group. The BACE1 activity of plasma samples (expressed as both $V_{\text{max}}$ and $V_{\text{mean}}$) exhibited an increase from HC subjects to MCI nonconverters, MCI converters, and finally to AD patients. *$p < .05$, **$p < .01$, and ***$p < .001$ compared with HC subjects. (B) Density scanning Western blot analysis of BACE1 protein expression in human plasma samples. Bars represent the relative protein expression as percentages of HC subjects (arbitrary unit of BACE1/Ponceau S). (C) Association between plasma BACE1 activity ($V_{\text{mean}}$, mFU/min) and BACE1 protein expression (ratio of BACE1 to Ponceau S). mFU, microfluorescence units.
there was no significant correlation found between BACE1 activity and CSF tau concentrations ($r = .18$) (Figure 3B) as well as CSF Aβ1-42 concentrations ($r = -.17$) (Figure 3C).

We also examined the association between BACE1 activity and cognition. MMSE scores were significantly lower in MCI converters and AD patients compared with scores in age-matched HC subjects and MCI nonconverters ($p < .001$) (Figure 4A). To assess the link between BACE1 activity and MMSE, we performed correlation analysis between BACE1 activity and MMSE across diagnoses (Figure 4B). In particular, we discovered a high overlap of BACE1 activity of 2 to 6 microfluorescence units (mFU)/min/μg $V_{\text{mean}}$ between HC subjects and MCI nonconverters, as shown in Figure 4B (green and yellow lines). Moreover, MCI converters (red line) and AD patients (blue line) exhibited a substantial overlap in BACE1 activity in the same range as shown in Figure 4B. We further found that all AD patients and MCI converters had values of BACE1 activity ($V_{\text{mean}}$) ≥2.6, while values of 2 to 6 mFU/min/μg of BACE1 activity were found in HC subjects ($V_{\text{mean}} < 2$) and MCI nonconverters ($V_{\text{mean}} < 6$). These findings demonstrate that plasma BACE1 enzymatic activity is highly correlated with cognitive functions.

**DISCUSSION**

To our knowledge, this is the first study that measures BACE1 enzymatic activity and protein expression in plasma samples of HC subjects, MCI converters to AD, MCI nonconverters, and patients with probable AD. First, we demonstrated that BACE1 exists as a functional enzyme in human plasma. Second, we found that BACE1 activity significantly increased in the plasma of patients with probable AD and individuals with...
Blood BACE1 Activity Predicts AD in MCI Subjects

We also identified cut-point values for BACE1 activity distinguishing HC subjects (Vmean < 2 mFU/min/μg) from MCI converters as well as AD patients (Vmean > 2.6 mFU/min/μg). Finally, we observed a correlation between plasma BACE1 enzymatic activity and cognitive function. This association has not been reported for other biomarker candidates previously tested and may be a potential target for the development of a surrogate biomarker (indicating clinical outcome in trials and early treatment).

Our data suggest a potential role for plasma BACE1 activity as a useful peripheral diagnostic and mechanistic biomarker in the prodromal cognitive decline to syndromal AD dementia continuum. Plasma BACE1 activity might be employed in disease-modifying clinical trials for subject screening, selection, and stratification as well as for validating target engagement and mechanism of action.

AD is characterized by a long asymptomatic stage (lasting a decade or more) and an initial prodromal symptomatic phase preceding the manifestation of overt AD dementia syndrome (3,46,47). Owing to the disappointing results of phase III trials of antiamyloid compounds tested in patients with mild to moderate AD dementia (46,48,49), the asymptomatic to prodromal stages are increasingly recognized as the most promising therapeutic window for interventions aimed at effectively modulating the underlying pathophysiological and early symptomatic progression of AD (3,46,48). Although no disease-modifying treatment for AD is currently available, searching for disease-related biomarkers reflecting key molecular mechanisms and predicting the progression and conversion to AD dementia becomes urgent as new therapeutic interventions are being developed and tested earlier in target populations (46,50).

Despite enormous efforts performed at an international level to standardize methods, CSF biomarkers have not yet achieved the widespread approval and availability necessary for diagnostic use in clinical practice. However, advanced blood (plasma/serum)-based technologies and biomarkers promise to provide a new class of noninvasive and easy-to-use tests suitable for global application, such as acting as a screening tool in large numbers of asymptomatic or prodromal individuals at risk for developing AD (39). In this respect, BACE1 is emerging as one of the most encouraging biomarker candidates owing to its crucial enzymatic activity involved in processing APP to produce Aβ peptides; in addition, BACE1 appears to be associated with synaptic function (51,52).

We developed and optimized a plasma-based assay to detect BACE1 enzymatic activity in human plasma samples characterized by high sensitivity and specificity (Figure 1). Moreover, we used both logistics and receiver operating characteristic analyses for BACE1 activity for AD patients, MCI converters, and MCI nonconverters compared with HC subjects. Data showed that sensitivities of BACE1 activity for AD patients, MCI converters, and MCI nonconverters are 86% to 88%, 86% to 88%, and 64% to 88%, respectively. Specificities are 86% to 88%, 86% to 88%, and 64% to 88% for AD patients, MCI converters, and MCI nonconverters, respectively. Besides our tests, several other BACE1 activity-based methods utilizing the combination of enzyme-linked immunoabsorbent assays with substrate cleavage analysis have been established for CSF. However, some of these methodological

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**Figure 1.** Correlations of clinical Mini-Mental State Examination (MMSE) scores with plasma beta-secretase 1 (BACE1) activity in healthy control (HC), mild cognitive impairment (MCI) nonconverter, MCI converter, and Alzheimer’s disease (AD) subgroups. (A) MMSE score alone in HC subjects, MCI nonconverters, MCI converters, and AD patients resulted in a significant difference between HC and MCI subgroups (**p < .001). (B) Distributions of BACE1 activity and correlations with MMSE scores in different diagnostic groups. The distributions of BACE1 activity among HC subjects, MCI nonconverters, MCI converters, and AD patients were plotted with MMSE scores. The green line shows the area of HC subject BACE1 activity, the yellow line shows the area of MCI nonconverter BACE1 activity, the red line shows MCI converter BACE1 activity, and the blue line shows the area of AD patient BACE1 activity. Both MCI converters and AD patients share highly overlapped BACE1 activity and MMSE scores.

MCI (including both MCI converters and MCI nonconverters) compared with HC subjects after adjusting for sex, age, and recruiting center. Third, individuals with MCI who converted to probable AD at clinical follow-up examinations exhibited significantly higher BACE1 activity than MCI nonconverters. Moreover, we found that both MCI-AD converters and probable AD patients exhibit significantly elevated BACE1 activity relative to HC and MCI nonconverter groups. These findings suggest that plasma BACE1 activity not only may be associated with AD risk and disease activity, but also may help predict progression from prodromal AD to probable AD dementia. Increased BACE1 activity presents a novel, pathophysiologically relevant, and easily accessible candidate biomarker (currently entering phase III of diagnostic development and validation) to support the detection of underlying AD pathophysiology and to predict conversion to AD. Such a novel dynamic plasma biomarker may represent a reliable indicator that improves early detection of the disease and facilitates the early initiation of disease-modifying treatments.
Blood BACE1 Activity Predicts AD in MCI Subjects

The general demographics of subject populations and multivariate regression analysis of association between plasma beta-secretase 1 (BACE1) activity ($V_{\text{max}}$, mFU/min/µg) and the clinical diagnosis from three independent clinical centers. While BACE1 activity is highly different between diagnoses, the generalized linear model showed no statistically significant associations between BACE1 activity and age or sex as well as centers.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HC (n = 53)</th>
<th>MCI (n = 96)</th>
<th>AD (n = 75)</th>
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<tr>
<td>Subjects by Site (DEU/USA/SWE), n</td>
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<td>49/9/38</td>
<td>50/10/15</td>
</tr>
<tr>
<td>Sex, Male/Female, n</td>
<td>25/28</td>
<td>45/51</td>
<td>25/50</td>
</tr>
<tr>
<td>Age, Years, Mean ± SE</td>
<td>68 ± 0.1</td>
<td>69.5 ± 0.1</td>
<td>73.84 ± 0.12</td>
</tr>
<tr>
<td>MMSE (0–30), Mean ± SE (Range)</td>
<td>29.65 ± 0.03 (28–30)</td>
<td>27.14 ± 0.03 (17–30)</td>
<td>22.80 ± 0.05 (13–29)</td>
</tr>
</tbody>
</table>

The general demographics of subject populations and multivariate regression analysis of association between plasma beta-secretase 1 (BACE1) activity ($V_{\text{max}}$, mFU/min/µg) and the clinical diagnosis from three independent clinical centers. While BACE1 activity is highly different between diagnoses, the generalized linear model showed no statistically significant associations between BACE1 activity and age or sex as well as centers.

Biological Psychiatry
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ARTICLE INFORMATION

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Blood BACE1 Activity Predicts AD in MCI Subjects
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