Higher BDNF serum levels predict slower cognitive decline in Alzheimer’s disease patients

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Abstract
The neurotrophin brain-derived neurotrophic factor (BDNF) plays a critical role in neuronal survival, synaptic plasticity, and memory. Several recent studies have demonstrated altered BDNF serum levels in Alzheimer’s disease (AD) patients. However, the association of BDNF serum levels with the rate of cognitive decline in AD patients is still unclear. We demonstrate that BDNF serum levels are significantly decreased in AD patients with fast cognitive decline [decrease of Mini-Mental State Examination (MMSE) score > 4/yr; n = 12] compared to AD patients with slow cognitive decline (decrease of MMSE score ≤ 4/yr, n = 28) and show a significant correlation with the rate of cognitive decline during 1 yr follow-up. These results suggest that higher BDNF serum levels are associated with a slower rate of cognitive decline in AD patients. Further longitudinal studies are necessary to elucidate the kinetics and the potential role of serum BDNF as a surrogate marker of disease progression in AD patients.

Introduction
Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by cognitive decline with loss of memory. The rate of cognitive decline in AD has been noted to vary significantly among patients, but little is known about the biological basis of these differences and about prognostic predictors (Kraemer et al. 1994). However, the assessment of how rapidly AD is progressing has important implications in clinical practice, since the rate of disease progression may be the most important factor in determining prognosis (Soto et al. 2008). A biological marker for rapid cognitive decline would be valuable because at-risk patients could be targeted early for pharmacological, medical, and psychosocial interventions designed to slow deterioration. In addition, identifying factors that influence the rate of cognitive decline in AD may help to better understand the underlying disease mechanisms and to develop new treatment strategies against AD.

Recently, there has been much research into the possible involvement of neurotrophins such as brain-derived neurotrophic factor (BDNF) in either pathogenesis or disease course of AD (Mattson et al. 2004). BDNF is critical for the function and survival of neurons that degenerate in AD and thus represents a potential neuroprotective agent useful in preventing neurodegeneration, as clearly demonstrated in animal models of AD (Nagahara et al. 2009). BDNF has been demonstrated to transit the blood–brain barrier (BBB) in both directions (Pan et al. 1998; Poduslo & Curran, 1996). Thus, BDNF serum levels may represent an important reserve pool for the brain.

Recent studies on BDNF serum levels in AD patients have produced conflicting data. Some studies have reported reduced serum levels of BDNF in patients with mild cognitive impairment (MCI) (Yu et al. 2008) and AD patients with mild dementia...
[mean Mini-Mental State Examination (MMSE) score (±S.D.) 23.6±1.6] (Laske et al. 2007) and moderate to severe dementia (MMSE 6.88±6.78) (Yasutake et al. 2006). In contrast, other studies showed no different BDNF serum levels in AD patients with mild to moderate dementia (MMSE 20.5±4.8) (O’Bryant et al. 2009) or even significantly increased BDNF serum concentrations in AD patients with early stages (MMSE 25.5±1.5) compared to AD patients with more severe stages (MMSE 13.3±4.2) of dementia (Laske et al. 2006), respectively, in MCI patients (MMSE 27.6±1.8) and AD patients with mild to moderate dementia (MMSE 18.0±6.38) compared to healthy controls (Angelucci et al. 2010). Regarding cognitive functioning, previous studies have demonstrated a positive association between BDNF blood levels and the cognitive performance in healthy older adults (Gunstad et al. 2008; Komulainen et al. 2008) and in AD patients (Laske et al. 2006). Li et al. (2009) have shown in a recent study that BDNF levels in CSF are also positively associated with cognitive function at baseline and at follow-up of ~3 yr duration in healthy older adults. In contrast, other studies failed to demonstrate a significant association between BDNF serum levels and MMSE scores in AD patients (Angelucci et al. 2010; Laske et al. 2007; O’Bryant et al. 2009; Yasutake et al. 2006). The reasons for these discrepancies are not known, probably reflecting differences in patient recruitment and stage of the disease.

To the best of our knowledge, the association of BDNF serum levels with the rate of cognitive decline in AD patients is still unclear. Given the substantial neuroprotective effects of BDNF in animal models of AD and the potential of BDNF to transit the BBB, we hypothesized that higher BDNF serum levels may be associated with a slower rate of cognitive decline in AD patients. To test this hypothesis, we examined the potential impact of BDNF serum levels on the clinical course of AD by dividing AD patients into those with slow vs. fast cognitive decline during 1 yr follow-up.

Materials and methods

Subjects

Forty AD outpatients from our Memory Clinic at the University Hospital of Psychiatry and Psychotherapy Tübingen were included in the study. AD patients fulfilled the criteria of ICD-10, DSM-IV and the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) for probable AD (McKhan et al. 1984). The clinical severity of cognitive impairment was assessed by MMSE (Folstein et al. 1975). In the present study, we examined AD patients with mild to moderate dementia [mean MMSE score (±S.D.) 18.9±4.1]. AD patients with current or a history of depression or psychosis, with major physical illness, alcohol or substance abuse or use of psychoactive medications were excluded from the study.

All the patients were followed up prospectively and were re-examined clinically 1 yr later (range 11–13 months). Among AD patients, 28 patients showed a slow cognitive decline (decrease of MMSE score ≤4/yr) and 12 patients displayed a fast cognitive decline (decrease of MMSE score >4/yr) (Table 1). We set the threshold at 4 points/yr according to a previously published paper by Doody et al. (2001).

The study was performed according to the ethical principles of the Declaration of Helsinki (sixth revision, 2008) and was approved by the local institutional ethics committee. We obtained written informed consent from AD patients themselves or by their legally authorized representatives.

Blood sampling

Peripheral venous blood was sampled into serum tubes between 08:00 and 09:00 hours (fasting state) in order to take in account a possible circadian rhythm. Tubes were immediately immersed in melting ice. To minimize the source of platelets, serum was centrifuged within 30 min after sampling and stored at –18°C until further analysis.

Measurement of BDNF serum concentration

Serum levels of BDNF were measured using an enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems GmbH, Germany) according to the manufacturer’s instructions. All samples and standards were measured in duplicate, and the means of the duplicates were used for statistical analyses. The detection limit for BDNF was 31.25 pg/ml. The intra- and inter-assay coefficients of variation were <10%.

Statistical analysis

All statistical analyses were performed using the statistical analysis software package SPSS 17.0 (Germany). The data are presented as the mean ± S.D. Significance for the results was set at p <0.05. Continuous variables were tested for normal distribution with the Kolmogorov–Smirnov test. The two-tailed t test was used to assess differences between two groups in case of normal distribution. The Mann–Whitney U test was
used to assess differences between two groups in case of non-normal distribution. Fisher’s exact test was used to compare two groups in case of categorical variables. We conducted bivariate correlation analysis (Spearman test) between age, MMSE scores, BMI, years of education and BDNF serum levels at baseline and the rate of cognitive decline during 1 yr follow-up. As the next step, we performed a multiple linear regression analysis in order to calculate the independent association of each identified significant factor with the rate of cognitive decline.

Results

The baseline demographic and laboratory parameters of AD patients with fast vs. slow cognitive decline are given in Table 1. All patients were prospectively followed up and clinically re-examined estimating the cognitive status with the help of MMSE examination 1 yr later (range 11–13 months). Among AD patients, 28 patients presented with a slow cognitive decline and 12 patients displayed a fast cognitive decline (Table 1). AD patients with fast cognitive decline showed significantly lower baseline BDNF serum levels compared to AD patients with slow cognitive decline [fast vs. slow cognitive decline (mean ± S.D.): 21.3 ± 6.0 vs. 27.8 ± 8.9 ng/ml; \( p = 0.026 \)] during 1 yr follow-up period (Fig. 1a).

The rate of cognitive decline (defined as the change \( \Delta \) of MMSE scores from baseline to 1 yr follow-up) was significantly associated with BDNF serum levels \( (r = 0.318, p = 0.046; \text{Fig. 1b}) \), age \( (r = 0.315, p = 0.040) \) and MMSE scores at baseline \( (r = -0.378, p = 0.012) \). According to a multiple linear regression analysis, BDNF serum levels \( (B = 0.390, p = 0.006) \), age \( (B = 0.608, p < 0.0001) \) and MMSE scores \( (B = -0.280, p = 0.042) \) at baseline were independent predictors for the rate of cognitive decline. These three factors together explained 53% of the corrected variance of the rate of cognitive decline.

Discussion

The major findings of the present study are: (1) baseline BDNF serum levels are significantly lower in AD patients with later fast cognitive decline compared to AD patients with later slow cognitive decline; (2) baseline BDNF serum levels are significantly and independently associated with the rate of cognitive decline in AD patients.

It has been reported that younger age and lower MMSE scores are associated with a faster cognitive decline in AD patients (Teri et al. 1995). In line with these findings, in the present study AD patients with fast cognitive decline are significantly younger than the slow cognitive decline group. As a novel, and counterintuitive finding of the present study, AD patients with fast cognitive decline have significantly higher baseline MMSE scores than the slow cognitive decline group. The reason for this discrepancy is not

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AD patients with slow cognitive decline (n = 28)</th>
<th>AD patients with fast cognitive decline (n = 12)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male, ( n )</td>
<td>21/7</td>
<td>5/7</td>
<td>0.071( ^a )</td>
</tr>
<tr>
<td>Age (years), mean ± S.D.</td>
<td>74.8 ± 7.7</td>
<td>71.8 ± 9.0</td>
<td>&lt;0.001( ^c )</td>
</tr>
<tr>
<td>Education (yr), mean ± S.D.</td>
<td>11.3 ± 3.1</td>
<td>11.8 ± 2.6</td>
<td>0.71( ^b )</td>
</tr>
<tr>
<td>MMSE, mean ± S.D.</td>
<td>18.1 ± 3.8</td>
<td>20.8 ± 4.4</td>
<td>&lt;0.0001( ^b )</td>
</tr>
<tr>
<td>Change MMSE baseline to 1 yr follow-up, mean ± S.D.</td>
<td>0.4 ± 2.7</td>
<td>-11.2 ± 4.4</td>
<td>&lt;0.001( ^b )</td>
</tr>
<tr>
<td>BMI, mean ± S.D.</td>
<td>24.4 ± 2.8</td>
<td>24.6 ± 3.7</td>
<td>0.587( ^c )</td>
</tr>
<tr>
<td>ChEI treatment, ( n ) (%)</td>
<td>22 (78.6)</td>
<td>10 (83.3)</td>
<td>1.0( ^a )</td>
</tr>
<tr>
<td>BDNF serum levels (ng/ml), mean ± S.D.</td>
<td>27.8 ± 8.9</td>
<td>21.3 ± 6.0</td>
<td>0.026( ^b )</td>
</tr>
</tbody>
</table>

MMSE, Mini-Mental State Examination; BMI, body mass index; ChEI, cholinesterase inhibitor.

\( ^a \) Fisher’s exact test.

\( ^b \) Two-tailed \( t \) test for unpaired samples.

\( ^c \) Mann–Whitney \( U \) test for unpaired samples.
known and may be related to the small sample size of the present study and other potential influencing factors such as education (Teri et al. 1995).

Several recent studies have examined the association between BDNF serum levels and cognitive functions in healthy older adults and in AD patients. Some studies demonstrated that higher BDNF serum levels were associated with better cognitive functions in healthy older adults (Gunstad et al. 2008; Komulainen et al. 2008) or AD patients (Laske et al. 2006). Gunstad et al. (2008) recruited 35 healthy older adults (age 60–85 yr) and found that higher BDNF serum levels were associated with better performance on the MMSE and short form of the Boston Naming Test. However, no significant association was found between BDNF serum levels and measures of learning and memory, attention and information processing speed, working memory, executive functioning, or verbal fluency, which may have been due to low power from the small sample size. Komulainen et al. (2008) analysed data from 1389 healthy older adults participating in the Dose–Responses to Exercise Training (DR’s EXTRA) Study (age 57–79 yr) and found decreased levels of plasma BDNF significantly associated with poorer CERAD (Consortium to Establish a Registry for Alzheimer’s Disease) neuropsychological test battery scores of confrontation naming, list learning, list recall, list recognition, and list savings for women, but not for men. In addition, Laske et al. (2006) have demonstrated a positive association between BDNF serum levels and MMSE scores in 30 AD patients ranging from mild to severe dementia (Laske et al. 2006). In contrast, other studies failed to show a significant association between BDNF serum levels and cognitive functions in MCI or AD patients (Angelucci et al. 2010; Laske et al. 2007; O’Bryant et al. 2009; Yasutake et al. 2006). Laske et al. (2007) analysed data from 27 AD patients with mild dementia and 28 age-matched controls and found no significant relationship between BDNF serum levels and MMSE scores, which was consistent with two independent investigations including 60 AD patients with moderate to severe dementia and 33 controls (Yasutake et al. 2006), respectively, 54 MCI patients, 89 AD patients with mild to moderate dementia and 27 healthy controls (Angelucci et al. 2010). In line with these negative findings, O’Bryant et al. (2009) failed to demonstrate any significant relationship between serum BDNF levels and MMSE or Clinical Dementia Rating (CDR) scores, analysing data from 196 participants (98 AD patients with mild to moderate dementia and 98 older controls) from the Texas Alzheimer’s Research Consortium (TARC). The reasons for these discrepancies are not known, probably reflecting differences in patient recruitment and stage of the disease. However, the association of BDNF serum levels with the rate of cognitive decline in AD patients is still unclear.

To clarify whether BDNF serum levels may have an impact on the clinical course of AD, we compared BDNF serum levels in AD patients with slow vs. fast cognitive decline defined after 1 yr follow-up period (* p < 0.05). (b) Correlation between change of Mini-Mental State Examination (MMSE) score after 1 yr and baseline BDNF serum levels in AD patients (r = 0.329, p = 0.038).

Fig. 1. (a) Boxplot showing brain-derived neurotrophic factor (BDNF) serum levels in Alzheimer’s disease (AD) patients with fast vs. slow cognitive decline defined after 1 yr follow-up period (* p < 0.05). (b) Correlation between change of Mini-Mental State Examination (MMSE) score after 1 yr and baseline BDNF serum levels in AD patients.
are associated with a slower rate of cognitive decline in AD patients. It is important to note, that platelets are the main source of BDNF in human blood (Fujimura et al. 2002). Thus, BDNF measurement in serum is likely to include BDNF stored in platelets and freely circulating BDNF. Further longitudinal studies are necessary to elucidate the kinetics and the potential role of serum BDNF as a surrogate marker of disease progression in AD patients. This finding could be of great clinical relevance, as early detection of AD patients at risk of rapid cognitive decline may allow early pharmacological, medical, and psychosocial interventions designed to slow deterioration.

BDNF plays a key role in modulating synaptic transmission and plasticity in the brain, important in the processes of learning and memory (Bekinschtein et al. 2008). The potential slowing impact of BDNF on the rate of cognitive decline in AD patients may also be due to its neuroprotective effects in the brain. A recent study has demonstrated substantial neuroprotective effects in rodent and primate animal models of AD, acting through amyloid-independent mechanisms (Nagahara et al. 2009). According to experimental data, BDNF protects against beta-amyloid (Aβ)-induced neurotoxicity (Arancibia et al. 2008) and may contribute to increased Aβ degradation by promoting the expression of somatostatin (Marmigère et al. 2001; Villuendas et al. 2001). In addition, BDNF is capable of inactivating glycogen synthase kinase-3beta (GSK-3β) (Foulstone et al. 1999), which is involved in hyperphosphorylation of tau protein (Leroy et al. 2002).

These findings point towards BDNF as a new treatment target in AD. Treatment strategies increasing BDNF serum levels could be useful for delaying the progression of AD. In previous studies we have shown that treatment with the acetylcholinesterase (AChE) inhibitor donepezil and lithium is paralleled with an increase of BDNF serum concentration in AD patients (Leyhe et al. 2008, 2009). Previous preclinical and clinical studies have suggested that lithium and donepezil exert neuroprotective and neurotrophic effects (Chuang & Manji, 2007; Noh et al. 2009). Thus, the increase of BDNF could be an important mechanism of how donepezil and lithium treatment exert their neuroprotective effects.

Conclusion

Our findings indicate that higher BDNF serum levels at baseline are associated with a slower rate of cognitive decline in AD patients during 1 yr follow-up, which may be due to its known neuroprotective effects in the brain. Thus, treatment strategies increasing BDNF serum levels could be useful for delaying the progression of AD. Further longitudinal studies are necessary to elucidate the kinetics and the potential role of serum BDNF as a surrogate marker of disease progression in AD patients.

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Statement of Interest

None.

References


