Low Circulating Acute Brain-Derived Neurotrophic Factor Levels Are Associated With Poor Long-Term Functional Outcome After Ischemic Stroke

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Abstract

Background and Purpose: Brain-derived neurotrophic factor (BDNF) plays important roles in brain plasticity and repair, and has been shown to influence stroke outcomes in animal models. Few clinical studies on BDNF in relation to ischemic stroke (IS) have been performed. The aims of the present study are to investigate whether acute circulating BDNF levels are: 1) altered in IS compared to controls; 2) associated with short- and long-term functional outcome after IS.

Methods: Serum levels of BDNF were analyzed in the Sahlgrenska Academy Study on Ischemic Stroke. Etiologic subtypes were defined according to the TOAST criteria. Functional outcome was assessed using the modified Rankin Scale at 3 months, 2 years and 7 years after stroke.

Results: Acute phase BDNF levels were significantly lower in IS cases (N=491) compared to controls (N=513), and this was true in all main etiological subtypes. Low BDNF levels were associated with poor functional outcome. During long-term follow-up this association was independent of traditional risk factors and initial stroke severity.

Conclusions: Circulating BDNF protein levels are lowered in the acute phase of stroke, and low levels are associated with poor long-term functional outcome. Further studies are necessary to confirm these associations and to determine the predictive value of BDNF in stroke outcomes.

INTRODUCTION:

Brain-derived neurotrophic factor (BDNF) has a documented role in neurogenesis[1] and influences functional motor recovery after an ischemic brain lesion in animal models.[2] _ENREF_3 Recently the prognostic value of circulating BDNF levels has received attention in some brain disorders including traumatic brain injury (TBI) and post-stroke depression (PSD). Acute serum BDNF levels were able to predict severity and outcome of a TBI, and patients with the lowest BDNF levels had the highest odds of incomplete recovery.[3] Similarly, stroke patients that developed PSD had low admission levels of serum BDNF.[4] No study has yet looked at BDNF proteins levels in relation to functional outcome after ischemic stroke (IS).

BDNF may play a role also outside the central nervous system (CNS), however, the source of peripheral levels remains to be determined. Levels of circulating BDNF correlate with several vascular risk factors[5-7], and low BDNF concentrations have recently been found to associate with an increased risk of incident stroke/TIA.[8] This study aimed to determine: 1) the concentration of BDNF in serum of IS patients and matched controls; 2) whether acute levels of BDNF are associated with short-term (3 months) and/or long-term (2 and 7 years) functional outcome after stroke.

METHODS:

Additional details can be found in the Online Supplement (please see http://stroke.ahajournals.org)

Study population, BDNF and outcome measurements

Participants were from the Sahlgrenska Academy Study on Ischemic Stroke (SAHLSIS), the design of which has been reported.[9] Serum samples were collected from 514 patients in the acute phase and from 514 matched controls. Surviving patients also underwent blood sampling at a 3-month follow-up. BDNF levels were measured using the BDNF E_{max} ImmunoAssay System (Promega, WI, USA). Functional outcome was assessed at 3 months, 2 years and 7 years post-stroke by the modified Rankin Scale (mRS). For the present study, 491 acute phase, 470 3-month, and 513 control samples were available for analysis.

Statistical analysis

Associations between BDNF and overall IS or TOAST subtypes were investigated using unconditional logistic regression analysis. Model A was adjusted for age and sex. Model B was additionally adjusted for hypertension, hyperlipidemia, diabetes mellitus, smoking status and atrial fibrillation.

Functional outcome (good, mRS 0-2 versus poor, mRS 3-6) was evaluated by binary logistic regression. A threshold analysis was pre-specified, wherein patients in the lowest tertile of BDNF, T1, were compared to persons in T2 + T3. Model A was adjusted for age and sex. Model B was additionally adjusted for cardiovascular risk factors, as well as initial stroke severity as measured by the Scandinavian Stroke Scale (SSS). Given that there are many confounding factors related to death after 7 years, patients that died were excluded from the primary analysis. All statistical analyses were performed using SPSS for Windows version 20 (IBM Corporation, NY, USA). The statistical significance level was 0.05 and *P*-values were two-tailed.

RESULTS:

Study sample

Baseline characteristics for SAHLSIS have been described previously.[9] The distribution of clinical characteristics for SAHLSIS based on BDNF tertiles (T1 versus T2-T3) are presented in the Online Supplement (Table I, please see http://stroke.ahajournals.org). Participants in T1 were significantly younger, had higher triglyceride levels, higher prevalence of atrial fibrillation, lower LDL cholesterol, lower blood pressure and lower prevalence of hypertension.

Association of BDNF serum levels and stroke/subtypes

Acute serum BDNF levels were significantly lower in IS patients compared to controls (geometric mean 18.3 ± 2.3 ng/ml vs 23.9 ± 1.5 ng/ml; $p<0.001$). In multivariable analyses, lower acute BDNF levels were independently associated with IS and each of the four main etiologic subtypes (Figure 1A). BDNF levels were lowest in patients with cardioembolic (CE) stroke. At 3-month follow up, BDNF levels were associated only with CE stroke (Figure 1B).

Association of BDNF and poor functional outcome

Acute BDNF levels were next analyzed in good (mRS 0-2) versus poor (mRS 3-6) functional outcome groups at 3 months, 2 years and 7 years post-stroke. The majority of patients that experienced poor outcome were in the lowest BDNF tertile, T1 (Figure 2A). In regression analyses, low BDNF levels were associated with poor functional outcome (Figure 2B). At 2 and 7 years post-stroke this association was independent of stroke severity and traditional risk factors.

DISCUSSION

Here we report that circulating BDNF levels are lower in the acute phase of IS in all etiologic subtypes compared to healthy controls. Patients with CE stroke had the lowest levels of BDNF, which remained significantly lower than controls at 3-month follow-up. While circulating BDNF levels are positively correlated to several risk factors for metabolic syndrome and cardiovascular dysfunction in healthy individuals[7], low concentrations have been observed in patients with several risk factors associated with stroke such as metabolic syndrome[10], type 2 diabetes mellitus[5], atrial fibrillation[8] and acute coronary syndromes.[6] Furthermore, low BDNF levels were recently demonstrated to be associated with an increased risk of incident stroke/TIA when adjusting for age, sex and traditional risk factors.[8] While the latter studies support our findings, the mechanism of decreased serum BDNF in acute stroke patients requires further study.

We also report that low acute levels of BDNF are associated with poor functional outcome up to 7-years after stroke. These data are in line with studies on TBI[3]. These findings are biological plausible because animal studies show that BDNF promotes neuronal remodeling and functional motor recovery after induction of a brain lesion.[2, 11] However, it is unclear whether circulating BDNF values measured in this study are representative of CNS values. Thus an alternative explanation is that BDNF affects outcome through peripheral mechanisms and/or is a marker for "something" that does.

Irrespectively, circulating BDNF values deserve further evaluation.

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CONFLICT OF INTEREST

None.

FIGURE LEGENDS

Figure 1: **A)** Odds ratios and 95% confidence intervals for ischemic stroke and subtypes per 1 SD increase in BDNF concentration. Model A adjusted for age and sex and Model B adjusted for traditional risk factors. Acute levels. **B)** As in panel B, but at 3-month follow-up. **P*<0.05, †*P*<0.01, ‡*P*<0.001

Figure 2. A) Percentage of patients in each BDNF tertile with good or bad outcome (defined as mRS 0-2 = good and mRS 3-6 = bad). **B)** Odds ratios and 95% confidence intervals for the association of BDNF protein levels (T1 versus T2-3) with poor functional outcome at 3 months, 2 years and 7 years post stroke. **P*<0.05 compared with good outcome after stroke.

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