Brief communication

BDNF genotype potentially modifying the association between incident stroke and depression

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Abstract

Objective: To investigate the role of the brain-derived neurotrophic factor (BDNF) gene val66met polymorphism in the association between stroke and depression.

Method: Five hundred community residents aged >65 years without stroke or depression at baseline were re-evaluated after 2 years. Disability (World Health Organization Disability Assessment Schedule, WHODAS II), cognitive function (Mini-Mental State Examination, MMSE), and BDNF genotype were also measured at baseline.

Results: The association between incident stroke and depression was strengthened progressively with increasing numbers of met alleles, and was only significant in subjects with the met/met genotype after adjustment for disability and cognitive function.

Conclusion: The BDNF val66met polymorphism may modify the association between stroke and depression.

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Keywords: Brain-derived neurotrophic factor; Stroke; Depression; Genetics

1. Introduction

Depression is common after stroke but is not fully accounted for by the location and volume of infarction or by the level of associated disability, and so causal pathways remain unclear (Robinson, 2003). A recent etiological hypothesis is that neurotoxic effects mediate depressive symptoms, while antidepressants have been shown to enhance neuroprotective effects (Manji et al., 2001). Brain-derived neurotrophic factor (BDNF), the most abundant neurotrophin in the brain, is one such neuroprotective protein. The BDNF gene is located on chromosome 11p14.1 and has several polymorphic markers. These include the single nucleotide polymorphism (SNP) at nucleotide 196 (G/A), which results in an amino acid substitution (valine to methionine) at codon 66 (val66met) (dbSNP number: rs6265) of the proBDNF molecule. This SNP affects intracellular processing and secretion of BDNF, and the met allele is associated with reduced BDNF activity (Egan et al., 2003). However, evidence for an association between the met allele and depression is inconsistent (Levinson, 2005). The BDNF gene may not be directly associated with depression, but instead may moderate the effect of environmental risk factors—for example, neuroprotective processes after stroke.

In a secondary analysis of data from a 2-year longitudinal study of a community population, we investigated the role of this polymorphism in modifying the association between stroke and depression.

2. Methods

Data were analysed from a community based prospective study of late-life psychiatric morbidity carried out in
Kwangju, South Korea from 2001 to 2003. The baseline cross-sectional survey carried out in 2001 has been described previously (Kim et al., 2004a,b). In brief, 732 community residents aged 65 years or over completed a fully structured diagnostic interview for depression of clinical importance (i.e. incorporating both moderate and severe depression) using the Geriatric Mental State diagnostic schedule (GMS B3) (Kim et al., 2003). The following potential risk factors for depression were recorded: (i) demographic data (age, gender, and education), (ii) disability using the Korean version of the second World Health Organization Disability Assessment Schedule (WHODAS II) (Kim et al., 2005), and (iii) cognitive function using the Korean version of the Mini-Mental State Examination (MMSE) (Park and Kwon, 1990). Follow-up evaluations were carried out in 2003 including the GMS B3, WHO DAS II, and MMSE assessments. The mean (S.D.) follow-up period was 2.4 (0.3) years. Self-reported diagnoses of and treatment histories for stroke were recorded on both occasions. Stroke was defined as present only if there was a clear history of sudden onset of unilateral paralysis, and/or loss of speech, and/or blindness lasting for at least 2 days, consistent with criteria used in the World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease (WHO MONICA) project (Thorvaldsen et al., 1997). BDNF genotypes were determined by previously described methods with minor modification (Proschel et al., 1992), and categorized as ‘val/val’, ‘val/met’, and ‘met/met’ genotypes.

At baseline evaluation, 83 (11.3%) of the 732 participants had depression, 34 (4.6%) had previous stroke, and 18 (2.5%) had both depression and stroke. The remaining 597 (81.6%) participants without depression or stroke formed the sample for this prospective analysis. Baseline characteristics of participants and non-participants at follow-up were compared using t-tests, χ² tests, or Mann–Whitney U-tests as appropriate. For estimating the strength of associations between incident stroke and incident depression, unadjusted and adjusted odds ratios (95% confidence intervals) were calculated controlling for potential confounding factors. Effect modification by BDNF genotype was investigated through stratified analyses. Statistical analyses were conducted with SPSS 12.0 software.

3. Results

Of 597 participants without stroke or depression at baseline, 500 (83.8%) completed all evaluations at the follow-up and comprised the analysed sample. Baseline characteristics of participants and non-participants at follow-up showed no substantial differences in demographic characteristics, disability, cognitive function, and BDNF genotypes between the two groups (Table 1). In both groups, no deviation from the Hardy–Weinberg equilibrium was observed (all p-values > 0.05). Of the 500 participants, 60 (12%) incident cases of GMS depression were identified, and 20 had incident stroke (53 depression alone, 13 stroke alone, 7 depression and stroke). Incident stroke by BDNF genotype was 2.5% for val/val, 3.4% for val/met, and 8.7% for met/met (p-value = 0.049). Incident depression by BDNF genotype was 13.6% for val/val, 11.5% for val/met, and 14.3% for met/met (p-value = 0.912).

The association between stroke and incident depression stratified by BDNF genotype strengthened progressively from val/val through val/met to met/met genotype (Table 2). Stroke was significantly associated with incident depression in participants with the met/met genotype, even after adjustment for potential confounding factors. However, the stroke × genotype interaction term fell below statistical significance (p-value = 0.171).

4. Discussion

As far as we are aware this is the first investigation to examine potential modifying effects of the BDNF val66met polymorphism on the association between stroke and depression in a community sample. Consistent with our hypothesis, the strength of association between incident stroke and depression increased incrementally with the number of met alleles, and was strongest in participants with the met/met genotype. However, results should be treated as preliminary findings in view of the fact that the interaction term did not reach statistical significance, and they require replication in a larger sample. If effect modification is confirmed, there are several possible explanations. First, accumulating

<table>
<thead>
<tr>
<th>Baseline status</th>
<th>Completed follow-up (n = 500)</th>
<th>Lost to follow-up (n = 97)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (S.D.) years</td>
<td>72.1 (5.4)</td>
<td>73.0 (6.9)</td>
<td>0.091</td>
</tr>
<tr>
<td>Gender, N (%) women</td>
<td>286 (57.2)</td>
<td>62 (63.9)</td>
<td>0.109</td>
</tr>
<tr>
<td>Education, median (IQR) years</td>
<td>2 (1–7)</td>
<td>2 (3–9)</td>
<td>0.365</td>
</tr>
<tr>
<td>WHODAS II, median (IQR) scores</td>
<td>2 (0–7)</td>
<td>3 (0–8)</td>
<td>0.336</td>
</tr>
<tr>
<td>MMSE, median (IQR) scores</td>
<td>24 (21–27)</td>
<td>25 (20–28)</td>
<td>0.522</td>
</tr>
<tr>
<td>BDNF genotypes, N (%) val/val</td>
<td>127 (25.4)</td>
<td>24 (24.7)</td>
<td>0.739</td>
</tr>
<tr>
<td>val/met</td>
<td>275 (55.0)</td>
<td>50 (51.5)</td>
<td></td>
</tr>
<tr>
<td>met/met</td>
<td>98 (19.6)</td>
<td>23 (23.7)</td>
<td></td>
</tr>
</tbody>
</table>

WHODAS, World Health Organization Disability Assessment Schedule II; MMSE, Mini-Mental State Examination; BDNF, brain-derived neurotrophic factor. 

* t-Test, χ² test, or Mann–Whitney U-test as appropriate.
Table 2
Associations between incident stroke and incident depression by BDNF genotype

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Unadjusted</th>
<th>Adjusted^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Total sample</td>
<td>500</td>
<td>2.33 (1.04–5.23)</td>
<td>0.035</td>
</tr>
<tr>
<td>By BDNF genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>val/val</td>
<td>127</td>
<td>1.95 (0.17–22.6)</td>
<td>0.586</td>
</tr>
<tr>
<td>val/met</td>
<td>275</td>
<td>2.89 (0.69–12.2)</td>
<td>0.164</td>
</tr>
<tr>
<td>met/met</td>
<td>98</td>
<td>8.94 (1.86–42.9)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

BDNF, brain-derived neurotrophic factor.

^a Adjusted for age, gender, education, disability, and cognitive function.

evidence has suggested that BDNF has an antidepressant effect (Duman et al., 1997). The met allele is associated with reduced BDNF activity (Egan et al., 2003), and might therefore confer increased vulnerability to the impact of stroke.

Second, BDNF appears to have survival-promoting actions on a variety of CNS structures including hippocampal, cortical, cholinergic, dopaminergic, and serotonergic neurons (Duman et al., 1997), and neuronal repair after stroke in brain regions associated with depression might be more delayed in those with the met allele. Third, BDNF has been reported to protect neurons against cerebral infarction (Yanamoto et al., 2004), so that the underlying impact of the stroke may be more severe in those with the met allele. Fourth, stroke often causes physical immobilization. In animal models, immobilization stress has been found to cause a marked reduction in BDNF expression in the hippocampus (Smith et al., 1995), which mediates depression.

Strengths of the study were that prospective data were obtained for both stroke and depression from a community population using a well-validated and fully structured diagnostic instrument for ascertaining depression of clinical importance. Follow-up rates were reasonable and there was no evidence of differential attrition. Institutions were not sampled in this study. However, provision of institutional care is very limited in South Korea, and particularly so in the region sampled. Most care for dependent people is carried out by cohabiting or nearby family members and we believe that the community sample will have captured a representative population of elders. A limitation of the study was that information on stroke relied on self-report information and corroboration by medical records or brain imaging was not feasible. It is possible that severe strokes might have been missed through inaccurate recall. Furthermore, the precise temporal relationship between stroke and depression during the follow-up period was not established, although most cases of post-stroke depression develop within 2 years (Robinson, 2003). It should also be borne in mind that there was limited power within this study to investigate effect modification in this way and confidence intervals were wide for the association of interest within BDNF genotype strata. Although the follow-up rate was relatively high for a community study, the cell sizes were small for some of the analyses and we cannot absolutely rule out an effect of differential attrition. A further important issue concerns the diagnosis of depression after stroke and the potential problem of false positive diagnosis because of an over-emphasis on vegetative symptoms. The GMS is potentially advantageous in this respect since, unlike DSM criteria, it was designed and validated for elderly populations where high rates of somatic comorbidity are expected. However, to our knowledge, it has not been specifically validated for the detection of depression after stroke and results in this respect should be treated with caution. Potential confounding factors which could not be addressed in this analysis include specific health conditions and medication use. However, we believe that these are unlikely to be associated to a substantial degree with BDNF genotype, and are therefore unlikely to explain the principal finding of interest.

Although there is a clear potential role for genetic factors in psychiatric disorders, these have been difficult to demonstrate (Hamer, 2002). The present findings provide preliminary evidence for a gene–environment interaction with respect to the impact of stroke on depression. Further replication is required in larger community samples and post-stroke cohorts.

Disclosure statement

The authors have no conflict of interest to declare with respect to this manuscript.

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References


