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Research report

Interactions between a serotonin transporter gene, life events and social support on suicidal ideation in Korean elders

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ABSTRACT

Introduction: The functional polymorphism in the serotonin transporter gene linked promoter region (5-HTTLPR) may modify associations between environmental stressors and suicidality in adolescents and working-age adults. We investigated whether the 5-HTTLPR *s*/*l* polymorphism interacts with stressful life events (SLEs) and social support deficits (SSDs) on late-life suicidal ideation.
Methods: 732 Korean community residents aged 65+ were evaluated and, of 639 without suicidal ideation, 579 (90.6%) were followed two years later. Prevalence and incidence of suicidal ideation was ascertained. Information on SLEs and SSDs were gathered, and covariates included socio-demographic characteristics, depressive symptoms, cognitive function, and disability.
Results: Significant interactions were observed between 5-HTTLPR genotype, SLEs and SSDs on both prevalence and incidence of suicidal ideation after adjustment for covariates. The associations of SLEs and SSDs with suicidal ideation were strengthened in combination with higher numbers of *s* alleles, and were only significant predictors in those with *s*/*s* genotype. A significant three-way interaction between 5-HTTLPR genotype, SLEs and SSDs was also found.
Limitations: The generalizability of suicidal ideation as a marker of suicidality should be considered.
Conclusions: Gene–environment interactions on suicidal behavior are therefore identifiable even in old age.

1. Introduction

Suicide rates are disproportionally higher in older adults than in the general population and are increasing with demographic ageing worldwide (Hawton and van Heeringen, 2009). The spectrum of suicidal behavior ranges from suicidal ideation through non-fatal attempts to completion (Beck et al., 1979). Understanding the etiology of suicidal behavior is an important step towards developing suicide prevention strategies.

Genetic predisposition is likely to be an important risk factor for suicidal behavior (Brezo et al., 2008). Relatives of people who have completed suicide have been found to have a ten-fold higher risk of suicidal behaviors than controls (Kim et al., 2005), and a meta-analysis of twin studies found a 175 times greater relative risk of suicide attempt/completion among monozygotic than dizygotic twins (Baldessarini and Hennen, 2004). Genes coding for components of the serotonin (5-HT) system have been studied widely as potential candidates underlying suicidal behavior (Brezo et al., 2008; Tsai et al., 2011). The 5-HT transporter (5-HTT) gene, located on chromosome 17q11.1–17q12, has received particular attention, since its product regulates serotonergic neurotransmission in the synapse. The most frequently studied variant is a biallelic polymorphism in the 5-HTT gene-linked promoter region (5-HTTLPR) for which short (*s*) and long (*l*) alleles, based on the presence or absence of a 43-base pair (bp) insertion/deletion, have been identified. The *s* allele is associated with reduced transcriptional activity and decreased gene expression (Heils et al., 1995), and is considered to be a candidate for a range of psychiatric disorders including suicidal behavior. Three meta-analyses concluded that the *s* allele is significantly involved in susceptibility to suicidal behavior (Anguelova et al., 2003; Lin and Tsai, 2004; Li and He, 2007). However, these studies raised questions about associated phenotypes, because the *s* allele appears to be associated only with particular suicidal behavior subtypes (Anguelova et al., 2003; Lin and Tsai, 2004).

Gene–environment interactions have received increasing attention in mental disorders, particularly in depression (Caspi and Moffitt, 2006). Although suicidal behavior is recognized to be complex and multifactorial (Mann, 2003), studies of gene–environment interactions

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have been rare. With respect to 5-HTTLPR, childhood adversities have been found to be more strongly associated with suicidal behavior in the presence of the *s* allele (Caspi et al., 2003; Gibb et al., 2006; Roy et al., 2007; Cicchetti et al., 2010), but not in all studies have found this (Coventry et al., 2010).

Most previous association and gene–environment interaction studies of suicidal behavior have been carried out in adolescent or adult populations (Li and He, 2007; Tsai et al., 2011). This line of investigation has not been pursued in elders, although biopsychosocial origins of suicidal behavior have been hypothesized to extend into late-life (Conwell et al., 2011). In addition, such studies have mainly examined childhood adversities as environmental risk factors, and have paid little attention to other important risks such as stressful life events and social support deficits (Conwell et al., 2011). To elucidate these questions further, we aimed to examine whether the 5-HTTLPR *s*/*l* polymorphism has individual effects and/or interactions with stressful life events and social support deficits on the prevalence and incidence of suicidal ideation in late-life, using data from a longitudinal study of an older Korean community population.

2. Materials and methods

2.1. Study overview and participants

This study analyzed data from a community based prospective survey of late-life psychiatric morbidity carried out in Kwangju, South Korea (Kim et al., 2007, 2011). At baseline, community residents aged 65 or over within two geographic catchment areas were identified from national registration lists and were approached to participate. Attempts were made to follow up all participants two years later (mean (SD) interval 2.4 (0.3) years). Suicidal ideation, stressful life events and social support deficits were examined both at baseline and at follow-up; and all the other data used here were obtained at baseline. All participants gave formal written informed consent at each examination. This study was approved by the Chonnam National University Hospital Institutional Review Board.

2.2. Suicidal ideation

The presence of suicidal ideation was identified using the questions from the community version of the GMS diagnostic schedule (GMS B3; Copeland et al., 1986) which was administered in identical format at both baseline and follow-up interviews. Participants were asked “Have you ever felt that you'd rather be dead? Have you ever felt you wanted to end it all? Have you ever felt killing yourself?” Reports of fleeting thoughts of suicide were ignored because they are not uncommon in elderly and may have little clinical significance (Copeland et al., 1986). If participants answered with a more obvious positive response, they were further asked “When was that? Have you felt like that in the last month?” Based on these questions, one month prevalence of suicidal ideation was identified both at baseline and at follow-up. For analysis of suicidal ideation ‘incidence’, the sample was restricted to those without suicidal ideation at baseline and suicidal ideation at follow-up was treated as a binary dependent variable.

2.3. 5-HTTLPR polymorphism

For genotyping, DNA was extracted from venous blood using standard procedures. Polymerase chain reaction (PCR) and the PCR-based restriction fragment length polymorphism assays were performed following previously published protocols with slight modification (Edenberg and Reynolds, 1998). Briefly, a PCR product was amplified using primers (5'-GGCGTTGCCGCTCTGAATGC-3', 5'-GAGGGACTGAGCTGGACAACCA-3') flanking the region containing the gene variation. The PCR conditions consisted of a 5 min denaturation step at 94 °C, 40 cycles of 30 s denaturation at 94 °C, 30 s annealing at 63 °C and 60 s extension at 72 °C, and a final 10 min extension step at 72 °C. PCR products were separated by electrophoresis in a 3% agarose gel stained with ethidium bromide and visualized by UV transillumination. The different genotypes were defined by the specific bands. The genotype was categorized as ‘*l*/*l*’, ‘*s*/*l*’, and ‘*s*/*s*’.

2.4. Stressful life events (SLEs) and social support deficits (SSDs)

Nine SLEs over the previous year of particular salience for late-life depression according to previous research (Prince et al., 1997) were enquired about: serious illness (self), serious illness (close relative), bereavement (immediate family), bereavement (other relative or close friend), marital separation, end of relationship, problem with close friend or relative, and theft or loss. Positive responses were totaled to generate a summary scale, and because of the skewed distribution, were divided into three groups (0, 1, and 2+). Six social support deficits that were likely to be salient to depression according to previous research (Prince et al., 1997), were also defined from answers to structured questions and categorized into the following binary variables: living alone, seeing a relative less often than once a month, seeing a friend less often than once a month, having no close friends, seeing a neighbor less often than once a month, and having no close neighbors. The items were then totaled to generate a summary scale, and, because of the skewed distribution were divided into three groups (0, 1, and 2+).

2.5. Other covariates

Sociodemographic and clinical characteristics potentially associated with suicidal ideation were considered. Data on age, gender, years of education, depressive symptoms, cognitive function and disability were obtained from the participant or their caregiver, as appropriate. Depressive symptoms were evaluated by the Geriatric Depression Scale (GDS), which does not include suicidal items (Yesavage et al., 1983). We purposefully did not use the GMS depression output as a covariate because of potential circularity (i.e. because suicidal ideation was ascertained from this instrument and contributed to the depression diagnostic algorithm). Cognitive function was evaluated using the Mini-Mental State Examination (MMSE; Folstein et al., 1975) and disability was assessed using the Korean version of the World Health Organization Disability Assessment Schedule II (WHODAS II; Kim et al., 2005).

2.6. Statistical analyses

Associations of 5-HTTLPR genotype, SLEs and SSDs with prevalent and incident suicidal ideation were measured initially in unadjusted analyses (χ^2 tests) and then further analyzed using multinomial logistic regression models adjusted for potential covariates. All covariates apart from gender were entered as continuous distributions. SLEs and SSDs analyzed were those recorded closest to the suicidal ideation outcome, at baseline or follow-up. The main effects of 5-HTTLPR genotype, SLEs and SSDs in these models were investigated, together with all possible two- and three-way interactions between them. Statistical analyses were carried out using SPSS 18.0 software.