Association between BDNF Val66Met polymorphism and generalized anxiety disorder and clinical characteristics in a Mexican population

A case–control study

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Abstract

The aim of the present case–control study was to explore the association between BDNF Val66Met (rs6265) polymorphism and generalized anxiety disorder in Mexican individuals, and whether this polymorphism plays a role in the symptomatology of anxiety.

A total of 212 subjects were included in the study. Around 75 patients with generalized anxiety disorder were diagnosed by psychiatrists based on the DSM-IV instrument and 137 unrelated subjects psychiatrically healthy were used as comparison group. The subclinical symptomatology in patients was assessed with the State-Trait Anxiety Inventory. BDNF rs6265 genotypes were analyzed using the polymerase chain reaction end-point method.

The association between BDNF Val66Met with the risk for generalized anxiety disorder was evaluated using 4 inheritance models. The present study showed that carrying the Met allele confers increased risk for the presence of generalized anxiety disorder ($\chi^2 = 4.7, P = .03$; OR (95%) 1.96 (1.05–3.56)) when patients with generalized anxiety disorder were compared with the comparison group.

Our results provide evidence of an association between the Val66Met polymorphism of the BDNF gene and generalized anxiety disorder in a Mexican population. However, no association was observed between this polymorphism and the symptomatology of anxiety.

Abbreviations: BDNF = brain-derived neurotrophic factor, BMI = body mass index, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, HDRS = Hamilton Depression Rating Scale in Spanish, HWE = Hardy–Weinberg equilibrium, PCR = polymerase chain reaction, SD = standard deviations, SNP = single nucleotide polymorphism, STAI = State-Trait Anxiety Inventory.

Keywords: BDNF, gene, generalized anxiety disorder, Mexican population

1. Introduction

Anxiety disorders are associated with impairments in academic, professional, social, and family functions of patients; these disorders are also related to the development of several psychopathologies.[1–11] Literature provides evidence that family history is one of the best established risk factors for anxiety disorders, with heritability estimates ranging from 20% to 40%.[4–6] Therefore, there is an urgent need to identify objective indicators or risk factors of anxiety disorders in order to understand their link to underlying biological mechanisms and treatments.[3,7] In this sense, the disruption in the regulation of emotion as a defining feature of anxiety disorders has been investigated. As a result, anxiety disorders have been associated with alterations in volume of amygdala and hippocampus of related prefrontal regions.[8,9] On the other hand, the brain-derived
neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors and it is concentrated in brain regions such as hippocampus and amygdala. Therefore, the BDNF gene has been involved in the pathophysiology of anxiety disorders.

With regard to studies analyzing the association between neuropsychiatric disorders and a genetic background, the most commonly used variant is the BDNF gene in humans. This gene comprises a single nucleotide polymorphism (SNP, rs6265) in which there is substitution of the amino acid valine (Val) to methionine (Met) at codon 66 (Val66Met). Furthermore, researchers had found that Met carriers were showed stronger neural responses to the emotional faces test and, in consequence, these authors suggested that this allele could affect important neural functions that correlate to anxiety and other psychopathologies.

Conversely, a number of studies have also found that the Val allele confers a risk for anxiety in case-control studies and family based investigations. In this sense, we performed an exploratory study and the aim of the present work was to: study the association between the BDNF Val66Met polymorphism and clinical characteristics such as depression and subclinical anxiety in a Mexican population.

2. Material and methods

2.1. Participants in the study

In the present study, a total of 75 patients (13 males, 62 females) were recruited; the mean age was 44.72 (SD 15.67) years old (range 18–80). Whereas in the comparison group (n = 137; males = 62 and females = 75) the mean age was 35.34 (SD 14.53) years old, with the same age range (18–80) years old. Patients were recruited at the General Hospital of Comalcalco in the city of Comalcalco in the state of Tabasco. All subjects were born in the municipality of Comalcalco. The comparison group was recruited at random when they attended the Carracci Medical Group in Mexico City.

2.2. Ethics statement

All subjects signed an informed consent to participate in the study. Previous to signing, the subjects received detailed explanation of the objective of the study. Their participation was voluntary and they did not receive any economic remuneration. This study was approved by both the DAMC-UJAT Ethics and Research Committee and the Ethics Committee of the General Hospital of Comalcalco (INV/259/C/1011).

2.3. Clinical evaluation

The patient group was diagnosed with generalized anxiety disorder between January and December, 2014. The diagnosis for the patients was based on the criteria of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) using the Mini-International Neuropsychiatric Interview. All subjects in the study were evaluated by a trained psychiatrist.

2.4. Assessment procedure for clinical variables

In the present study, sociodemographic characteristics such as gender, age, and level of education, were collected using a structured questionnaire. All subjects were measured for height in meters (m) and weight in kilograms (kg) using a digital scale. The body mass index (BMI) of each person was calculated as height squared (m²) divided by his/her weight (kg).

To analyze the association between BDNF Val66Met and clinical variables, we tested for depression and subclinical anxiety. To measure depression the Hamilton Depression Rating Scale in Spanish (HDRS) was used. The HDRS in Spanish has been validated and the Spanish version is widely used in research studies as well as in public health service in Tabasco. The HDRS comprises 17 items designed to assess the severity of depression with scores ranging from 0 to 21. To assess subclinical anxiety, we used the State-Trait Anxiety Inventory (STAI). This instrument has been validated in Spanish and this version has shown viability and validity in its use.

2.5. BDNF Val66Met (rs6265) genotyping

Genomic DNA was extracted from peripheral blood leukocytes using the modified Lahiri and Nurnberger method. The BDNF Val66Met (rs6265) was genotyped using a polymerase chain reaction (PCR) end-point method. As it has been previously reported we used 5 μL of final volume. We used 5 exonuclease TaqMan genotyping assays (C_11592758_10). The intensity of the fluorescence was measured with a 7500 Real-Time PCR system using the v2.1 software (Applied Biosystems). We performed the genotyping blind to patients or comparison group. As a quality control, we genotyped 20 samples in duplicate.

2.6. Statistical analysis

Data are presented as numbers with frequencies and percentages for categorical variables. The demographic description (years of age, years of schooling) and anthropometric variable (body mass index) are continuous variables and are presented as means and standard deviations (SD). We tested the Hardy–Weinberg equilibrium (HWE) using a Pearson’s goodness-of-fit chi-squared test. We used the chi-squared test to compare genotype and allele frequency between the group of patients and the comparison group. The same analysis was used in a comparison between BDNF Val66Met and anxiety disorder was carried out by gender. Association analyses among BDNF Val66Met polymorphism and demographic, anthropometric and clinical (HDRS, STAI-Y1, STAI-Y2) characteristics were performed with variance analysis (ANOVA), using the SPSS statistical software version 20.0. Significance level was set at P < .05.

3. Results

3.1. Characteristics of the population in the study

The socio-demographic features of cases and comparison groups are summarized in Table 1. We observed predominance in the number of females in the group of patients. Characteristics as age, level of education and body mass index between cases and controls were statistically different (Table 1).

3.2. Allele and genotype frequencies

In the present study, the genotype frequencies of BDNF Val66Met in patients (P-value = 0.34) and control (P-value = 0.77) groups satisfied the HWE.
The distribution of alleles and genotypes in the overall sample, patient group and comparison group subdivided by gender is presented in Table 1. No significant association was observed between the study group and the comparison group for genotype ($x^2 = 4.57, P = .10$). However, a statistical significance was observed for allele ($x^2 = 4.7, P = .03; OR (95%) 1.96 (1.05–3.56)$). When we performed an analysis by gender, no differences were observed in the frequencies for genotype and alleles. In addition, the inheritance hypothesis was tested according to 4 models: codominant, dominant, recessive and overdominant. However, none of the inheritance models was associated with an increased risk for developing anxiety disorders (Table 3).

### 3.3. Clinical characteristics by genotype

Finally, the present study analyzed the socio-demographic and clinical characteristics of the patients distributed by genotypes (Table 4). However, no significant differences were observed when we analyzed the socio-demographic characteristics, presence of depression, or characteristics such as state and trait of anxiety in patients. These results suggest that BDNF Val66Met...
does not influence depression or characteristics of anxiety in patients with anxiety disorders (Table 4).

### 4. Discussion

We studied the association between the *BDNF Val66Met* polymorphism and generalized anxiety disorder patients and healthy controls. Subsequently, we investigated whether the *BDNF Val66Met* polymorphism may influence socio-demographic and clinical characteristics, as well as the state and trait of anxiety in a Mexican population. To our knowledge, this is the first study examining the impact of this SNP in a Mexican community sample. Anxiety disorders have attracted special attention for their high prevalence. Due to their predominance, these disorders may serve as predictors for the development of other mental diseases such as bipolar disorder.\(^4\)\(^,\)\(^28\) Some evidence suggests that genetic factors may influence the vulnerability to develop anxiety disorders. The *BDNF* gene has been implicated in the pathophysiology of these disorders given that it plays a key role in memory and anxiety in the brain.\(^\)\(^4\)\(^,\)\(^29\)\(^,\)\(^30\)

Anxiety disorders were the sixth leading cause of disability in terms of YLDS (years of life lived with disability), in high- or middle-income countries.\(^\)\(^31\) Moreover, in another report was observed a global current prevalence of anxiety disorder of 7.3% (4.8%–10.9%) and ranged from 5.3% (3.5%–8.1%) in African cultures to 10.4% (7.0–15.5%) in Euro/Anglo cultures.\(^32\) In Mexico the anxiety disorder has been addressed as one of the principal disorders of the ICD-10. In fact, the National Survey of Psychiatric Epidemiology (ENEP) analyzed by Medina-Mora et al.\(^33\) was shown that about 28.6% of the population presented some of the 23 disorders of the ICD-10 at some time in their life. By type of disorders, the most frequent were those of anxiety (14.3% at some time in life), followed by substance use disorders (9.2%) and affective disorders (9.1%). In fact, anxiety disorders are more frequently observed in females (prevalence = 1.6) than in males (prevalence = 0.7) according to the data.\(^33\)

The present study showed that carrying the Met allele confers an increased risk for having an anxiety disorder in the population selected from the southeast of Mexico. The Met allele of this SNP has been associated with volume reduction in areas involved in the regulation of cognitive and emotional behavior such as hippocampus, prefrontal cortex, and amygdala in the brain.\(^\)\(^34\)\(^,\)\(^35\)

In agreement with our findings, Moreira et al.\(^36\) showed a significant association between the Met allele and risk of generalized anxiety disorder. Tocchetti et al.\(^37\) investigated the association of the *BDNF* polymorphism and anxiety disorders in children and adolescents, and logistic regression analysis showed that carrying one copy of the Met allele confers increased risk of presenting an anxiety disorder. Jiang et al.\(^38\) tested the relationship of this variant in single allele-based association studies with psychiatric diagnoses and personality measures. The Tridimensional Personality Questionnaire was administered to measure anxious temperament (harm avoidance and novelty seeking). They reported that individuals with the Met 66 allele were associated with increased harm avoidance and this allele was most abundant in individuals with both anxiety disorders and major depression. Furthermore, other results of genetic association in previous studies showed evidence that *BDNF* plays an important role in the pathophysiology of anxiety.\(^\)\(^39\)\(^,\)\(^40\)

When we assessed the association between the *BDNF Val66Met* polymorphism and socio-demographic and clinical characteristics of patients, it was not possible to observe any association between *BDNF* in the clinical data of Mexican patients and generalized anxiety disorder. The *BDNF Val66Met* polymorphism has been associated with obesity in patients suffering from a psychiatric disease.\(^41\) Therefore, the lack of association reported in various studies could be explained considering that *BDNF* may be acting in conjunction with other “hypothetical” genes or with genes that contribute to the clinical characteristics of certain psychiatric diseases.\(^\)\(^42\)\(^,\)\(^43\) Second, it is important to take into account that the frequency of *BDNF* alleles differs among populations.\(^44\)\(^,\)\(^45\)

Finally, some limitations of this study should be mentioned. First, the sample size is relatively small; therefore, these data need to be confirmed in a much larger sample in order to have a strong supportive evidence of the findings. Second, we did not include the early experience of patients and other environmental factors. *BDNF Val66Met* could be related to these characteristics of patients. Third, we did not consider other factors that could exert an influence on symptoms, such as psychiatric comorbidity which may represent one challenge for genetic studies.\(^\)\(^46\)\(^,\)\(^47\) Finally, we recognized there is genetic heterogeneity among Mexican population. Then, to reduce ethnic variation, we only included individuals with Mexican descent (Mexican parents and Mexican grandparents). Hence, at the light of these limitations caution must be taken by readers when generalizing our results.

### 5. Conclusions

The findings of this study showed that the Met allele of the *BDNF Val66Met* polymorphism may be involved in the generalized anxiety disorder in a sample of Southeast Mexican population. Similarly, no association between this polymorphism and clinical characteristics such as depression and subclinical anxiety was established in this Mexican population. However, due to the above mentioned limitations, our results must be interpreted with caution. The conduction of similar studies with larger samples is needed to confirm the present findings.

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**Table 4**

| Characteristics (Mean ± SD) | Val-Val (n = 61) | Val-Met (n = 13) | Met-Met (n = 1) | Overall sample | F     | P-value |
|-----------------------------|-----------------|-----------------|----------------|---------------|-------|---------|
| Education Level, years      | 7.03 ± 5.99     | 7.00 ± 4.08     | 6.00           | 7.01 ± 5.64   | 0.01  | .98     |
| Age, years                  | 44.11 ± 15.58   | 45.23 ± 17.75   | 57             | 44.72 ± 15.81 | 0.31  | .73     |
| Body mass index             | 27.68 ± 5.01    | 29.34 ± 2.80    | 33.3           | 28.04 ± 4.73  | 1.30  | .27     |
| Depression (HDRS)           | 15.69 ± 6.90    | 14.92 ± 5.22    | 15.00          | 15.55 ± 6.57  | 0.07  | .92     |
| STAI trait                  | 35.59 ± 8.73    | 37.92 ± 10.36   | 44.00          | 36.11 ± 8.99  | 0.74  | .47     |
| STAI state                  | 35.52 ± 9.21    | 39.54 ± 11.96   | 36.00          | 36.23 ± 9.71  | 0.91  | .40     |

*HDRS = Hamilton Depression Rating Scale in Spanish, STAI = State-Trait Anxiety Inventory.*
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