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Serum GDNF levels and anxiety disorders in a population-based study of young adults

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ABSTRACT

Objective: The aim of this study was to verify the serum GDNF levels in individuals with anxiety disorder (AD) in a population-based study.
Methods: This was a cross-sectional study population-based, with people aged 18 to 35. AD's assessment was performed using the Mini International Neuropsychiatric Interview (M.I.N.I). Serum GDNF was measured by ELISA using a commercial kit.
Results: The prevalence was 3.3% for post-traumatic stress disorder, 6.7% for panic disorders, 17% generalized anxiety disorder, 5.1% for obsessive- compulsive disorder and 7.5% for social phobia. Serum GDNF levels was higher in individuals with panic disorders ($p = 0.013$), generalized anxiety ($p = 0.035$), obsessive- compulsive disorder ($p = 0.005$) and social phobia ($p = 0.004$), when compared to individuals without ADs. Only post traumatic stress disorder is not associated with serum GDNF levels ($p = 0.119$).
Conclusion: In this paper, we observed increased serum levels of GDNF in individuals with anxiety disorders, suggesting that this biomarker can be used as a putative marker for AD's. The knowledge of the physiological changes related to anxiety disorders can provide a better understanding of AD's pathogenesis, as well as, mechanisms involved in the progression of this condition.

1. Introduction

Anxiety disorders (ADs) are one of the most prevalent and disabling mental health conditions, with lifetime prevalence estimates of 28.8% [1, 2]. They are associated with a considerable degree of social impairment, and an enormous economic burden for society [3]. ADs include a collection of syndromes characterized by exaggerated fear responses to perceived threats. Such threats extend to a wide range of situations in Generalized Anxiety Disorder (GAD) [4]. Furthermore, people diagnosed with anxiety disorders show an increased risk of death when compared to general population or people without mental disorders [5].

The ethiology and physiopathological hallmarks of anxiety are still under deep scrutiny, particularly regarding psychogenic and biological causes, which may mechanistically involve alterations in neurotrophic signalling. Recent studies have extensively investigated brain-derived neurotrophic factor (BDNF) demonstrating association with depression [6], bipolar disorders [7], anxiety disorders [8, 9]. Albeit, to our knowledge, there are few studies concerning the ethiopathological involvement of glial cell line-derived neurotrophic factor (GDNF) in these disorders. GDNF is a neurotrophic factor that is widely distributed in the central nervous system (CNS) [10]. It has been associated with key roles for cognitive function, such as synaptogenesis, synaptic plasticity, neurogenesis, neuronal growth, survival and maintenance of neurons, especially both serotonergic and dopaminergic neurons [11, 12]. Also, interestingly GDNF has been shown to have a protective effect against neurotoxic dopaminergic depletion induced by methamphetamine, which may be taken in account when considered the high prevalence of anxiety disorders among methanphetamine dependent adults [13].

Recently, GDNF has been assiociated with crucial roles in the pathophysiology of mood disorders. Recent studies indicated altered GDNF levels in individuals with mood disorders, however, studies

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revealed contradictory results. Both reduced [14] and elevated [15, 16] GDNF levels have been reported. Fontenelle et al. [17], found that patients with OCD exhibited significantly lower levels of BDNF and significant increased levels of NGF as compared with population controls. However, regarding GDNF the authors did not found difference [17]. Similarly, patients with generalized anxiety disorder (GAD) showed increases in the NGF plasma levels, which are partially reverted by the psychological treatment. However, GDNF plasma levels were not assessed [18].

Previous literature has demonstrated the GDNF involvement in several psychiatrics disorders, including anxiety disorders. However, there are few and contradictory studies evaluating the GDNF levels in the anxiety disorders. Thus, since this neurotrophic factor has a relevant role in neuroprotection, the aim of this study was to verify the serum GDNF levels in individuals with anxiety disorder in a population-based study with young adults.

2. Material and methods

2.1. Study population

This was a cross-sectional study, nested in a population-based study of people aged 18 to 35, living in Pelotas (Brazil), in the period from June 2011 to October 2012. Sample selection was performed by multistage clusters, considering the census division of the city (Pelotas) in 2010 with population of 97,000 individuals in that age range in the current census of 495 sectors in the city (*IBGE—Instituto Brasileiro de Geografia e Estatística;* (http://www.ibge.gov.br).

All participants agreed to participate in the study by providing their free and informed consent. The study was approved by the Catholic University of Pelotas Ethics Committee (2010/15).

2.2. Instruments

The subjects signed an informed consent and answered a questionnaire on demographic information. Socioeconomic evaluation was assessed with the National Economic Index considering material assets and schooling of the head of the household [19]. The participants also answered about use of tobacco and psychiatric drugs. To evaluate alcohol use disorder, the participants also responded to the CAGE questionnaire [20].

The Mini International Neuropsychiatric Interview (M.I.N.I.) was performed to all participants by well-trained psychologists. This is a short-structured interview, lasting around 15–30 min, designed for use in clinical practice and research, with the goal of adequating the interview according to DSM-IV criteria. The version used here is the MINI 5.0 in Portuguese, which was developed for use in primary care and clinical trials. The M.I.N.I. has psychometric qualities comparable to other longer and more complex standardized diagnostic questionnaires, with sensitivity and specificity of 0.92. Concerning the diagnosis of anxiety disorders, agreement (Kappa) was higher than 0.50 for all the diagnoses explored.

Moreover, this instrument is made up of independent diagnostic modules with the objective of reducing interview time [21]. For this present study, we used the modules for anxiety disorder, psychotic symptoms and current major depressive disorder (MDD). Regarding current anxiety disorder, we evaluated: social phobia, Post-Traumatic Stress Disorder (PTSD), obsessive–compulsive disorder (OCD), Panic disorders and generalized anxiety disorder (GAD). Psychotic symptoms and MDD modules were evaluated with the intention of excluding individuals who presented these diagnoses. Thus, for the aim of present study, we have excluded individuals diagnosed with MDD or who presented any psychotic disorder, besides individuals were taking psychiatric drugs were also excluded from the study.

2.3. Body mass index

Anthropometric measurements were taken for the evaluation of body mass index (BMI). Height was measured without shoes to the nearest 0.1 cm. Weight was measured in kilograms to the nearest 0.1 kg. BMI was calculated as the weight (in kilograms) and height (in meters), according to the formula: Kg/m^2 [28].

2.4. Biochemical analysis

For the biochemical analyses, 10 ml of blood was collected from each subject by venipuncture, into an anticoagulant-free vacuum tube, after the interview, between 8:00 AM and 11:00 AM. The blood was immediately centrifuged at 4000 $\times g$ for 10 min, and the serum was kept frozen at −80 °C until analysis. Serum GDNF levels were measured with a sandwich-ELISA immunoassay kit according to the manufacturer's instructions (DuoSet ELISA Development, R&D Systems, Inc., USA) and data expressed in pg/mL.

2.5. Data analysis

Statistical analyses were performed using the Statistical Program for Social Sciences (SPSS) 21.0 (IBM Corporation, Armonk, NY) and the Graph Pad Prism 6.0 (GraphPad Software Inc., San Diego, USA). The serum GDNF levels had non-Gaussian distributions. Considering the nonparametric nature of obtained data, we utilized Mann–Whitney, Kruskal–Wallis tests, and the Spearman's correlation tests. Serum GDNF levels were presented as median and interquartile range. A linear regression analysis was applied to control for possible confounding factors, with a p-value of ≤0.2 in the bivariate analyses. For this, serum GDNF levels were logarithmically transformed before the statistical analysis. The results with p-values of ≤0.05 were considered statistically significant.

3. Results

The total sample comprised 938 young adults, of these: 55.4% were women, with mean age of 26.06 ± 5.11 years; 76.4% were Caucasian; 24.3% were tobacco users, and 12.4% were identified with alcohol abuse/dependence. In relation of anxiety disorders, 31 (3.3%) subjects were diagnosed with PTSD, 63 (6.7%) with panic disorders, 159 (17.0%) with GAD, 48 (5.1%) with OCD, and 70 (7.5%) with social phobia. In Table 1, the serum GDNF levels are shown in accordance with the sociodemographic and clinical characteristics of the sample. Curiously, in our study, GDNF levels were associated with alcohol use (p = 0.012).

Regarding anxiety disorders, only PTSD is not associated with alterations in serum GDNF levels (p = 0.119; Fig. 1A). Other disorders showed a significantly higher serum GDNF levels when compared to healthy control patients: panic disorders (p = 0.013; Fig. 1B); GAD (p = 0.035; Fig. 1C); OCD (p = 0.005; Fig. 1D); and Social Phobia (p = 0.004; Fig.1E).

To assess the influence of possible confounding factors, interfering in the results, an adjusted analysis (linear regression) was performed, including age, BMI, tobacco use, and alcohol use. These analyses showed that none of these variables did interfere with the observed results, when regarding the panic disorders (p = 0.043; B = 0.108; CI: 0.38–0.261), GAD (p = 0.038; B = 0.203; CI: 0.52–0.190), OCD (p = 0.001; B = 0.108; CI: 0.68–0.202), and social phobia (p = 0.044; B = 0.130; CI: 0.53–0.143).

4. Discussion

In this study, we tested the hypothesis that serum GDNF levels could be associated in different subtypes of anxiety disorders. In this sense, we sought to investigate an association between the serum GDNF levels in